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 NEWS  3  Feb 06   Engineering Information Encompass files have new names
 NEWS  4  Feb 16   TOXLINE no longer being updated
 NEWS  5  Apr 23   Search Derwent WPINDEX by chemical structure
 NEWS  6  Apr 23   PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
 NEWS  7  May 07   DGENE Reload
 NEWS  8  Jun 20   Published patent applications (A1) are now in USPATFULL
 NEWS  9  JUL 13   New SDI alert frequency now available in Derwent's
                   DWPI and DPCI
 NEWS 10  Aug 23   In-process records and more frequent updates now in
                   MEDLINE
 NEWS 11  Aug 23   PAGE IMAGES FOR 1947-1966 RECORDS IN CAPLUS AND CA
 NEWS 12  Aug 23   Adis Newsletters (ADISNEWS) now available on STN

 NEWS EXPRESS  August 15 CURRENT WINDOWS VERSION IS V6.0c,
               CURRENT MACINTOSH VERSION IS V6.0 (ENG) AND V6.0J (JP),
               AND CURRENT DISCOVER FILE IS DATED 07 AUGUST 2001
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FILE 'USPATFULL' ENTERED AT 10:37:58 ON 06 SEP 2001
CA INDEXING COPYRIGHT (C) 2001 AMERICAN CHEMICAL SOCIETY (ACS)

=> s ziprasidone sulfone
L1            4 ZIPRASIDONE SULFONE

=> dup rem l1
PROCESSING COMPLETED FOR L1
L2            4 DUP REM L1 (0 DUPLICATES REMOVED)

=> d l2 ab

L2   ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2001 ACS
AB   The invention relates to novel methods using, and pharmaceutical compns.
     comprising ziprasidone metabolites.  The methods and compns. of the
     invention are suitable for the treatment of neuroleptic and related
     disorders.  Ziprasidone sulfoxide and ziprasidone
     sulfone are prepd., their 5-HT2 and dopamine D2 receptor activity
     studied, and dosage forms contg. the compds. are presented.


=> d l2 1 all

L2   ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2001 ACS
AN   2000:725450  CAPLUS
DN   133:276365
TI   Ziprasidone metabolite compositions for the treatment of neuroleptic and
     related disorders
IN   Barberich, Timothy J.; Rubin, Paul D.; Yelle, William E.
PA   Sepracor Inc., USA
SO   PCT Int. Appl., 27 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
IC   ICM  A61K031-00
CC   1-11 (Pharmacology)
     Section cross-reference(s): 28, 63
FAN.CNT 1
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
PI   WO 2000059489      A2   20001012       WO 2000-US8707   20000331
     WO 2000059489      A3   20010525
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR,
             CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
             ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
             LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,
             SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW,
             AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
             DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
             CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRAI US 1999-127939     P    19990406
```

AB The invention relates to novel methods using, and pharmaceutical compns. comprising ziprasidone metabolites. The methods and compns. of the invention are suitable for the treatment of neuroleptic and related disorders. Ziprasidone sulfoxide and **ziprasidone sulfone** are prepd., their 5-HT2 and dopamine D2 receptor activity studied, and dosage forms contg. the compds. are presented.

ST ziprasidone metabolite pharmaceutical neuroleptic disorder

IT 5-HT receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(5-HT2A; ziprasidone metabolite compns. for the treatment of neuroleptic and related disorders)

IT Tachykinin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NK antagonists; ziprasidone metabolite compns. for the treatment of neuroleptic and related disorders)

IT Analgesics
(cholinergic; ziprasidone metabolite compns. for the treatment of neuroleptic and related disorders)

IT Antidepressants
(tricyclic; ziprasidone metabolite compns. for the treatment of neuroleptic and related disorders)

IT 5-HT agonists
Adrenoceptor agonists
Anticonvulsants
Drug delivery systems
Oxidizing agents
Psychotropics
Tranquilizers
(ziprasidone metabolite compns. for the treatment of neuroleptic and related disorders)

IT 50-67-9, Serotonin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(agonists and reuptake inhibitors; ziprasidone metabolite compns. for the treatment of neuroleptic and related disorders)

IT 9002-17-9, Xanthine oxidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; ziprasidone metabolite compns. for the treatment of neuroleptic and related disorders)

IT 188797-77-5P, **Ziprasidone sulfone** 188797-80-0P, Ziprasidone sulfoxide
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(ziprasidone metabolite compns. for the treatment of neuroleptic and related disorders)

IT 21563-00-8, Gold chloride
RL: CAT (Catalyst use); USES (Uses)
(ziprasidone metabolite compns. for the treatment of neuroleptic and related disorders)

IT 50-47-5, Desipramine- 50-48-6 50-49-7, Imipramine- 50-78-2, Aspirin 53-86-1, Indomethacin 60-99-1, Methotrimeprazine 72-69-5, Nortriptyline 99-66-1 103-90-2, Acetaminophen 298-46-4, Carbamazepine 315-30-0, Allopurinol 361-37-5, Methysergide 22071-15-4, Ketoprofen 54910-89-3, Fluoxetine 61869-08-7, Paroxetine 74103-06-3, Ketorolac 79617-96-2, Sertraline 93413-69-5, Venlafaxine 116539-59-4, Duloxetine
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ziprasidone metabolite compns. for the treatment of neuroleptic and related disorders)

IT 7681-52-9, Sodium hypochlorite 7697-37-2, Nitric acid, reactions
7722-64-7, Potassium permanganate 7722-84-1, Hydrogen peroxide, reactions 7778-54-3, Calcium hypochlorite 7790-28-5, Sodium periodate 10058-23-8, Potassium hydrogen persulfate 10139-51-2, Ceric ammonium nitrate 11138-47-9, Sodium perborate 87691-87-0,
1-(1,2-Benzisothiazol-3-yl)piperazine 118289-55-7, 6-Chloro-5-(2-chloroethyl)oxindole
RL: RCT (Reactant)
(ziprasidone metabolite compns. for the treatment of neuroleptic and related disorders)

IT 146939-27-7P, Ziprasidone
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(ziprasidone metabolite compns. for the treatment of neuroleptic and related disorders)

=> d 2-4 ab

L2 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2001 ACS

AB The aim of this study was to identify the cytochrome P 450 (CYP) isoform(s) responsible for the formation of the primary metabolite of ziprasidone (ziprasidone sulfoxide), to det. the kinetics of its formation and to predict possible drug interactions by investigating CYP isoform inhibition in an in vitro study. Methods In vitro metab. of [14C]-ziprasidone was studied using human liver microsomes. The metabolites were identified using mass spectrometry. The kinetics of metabolite formation were detd. using [14C]-ziprasidone (10-200 .mu.M) over 5 min, and Km and Vmax were estd. from Lineweaver-Burk plots. IC50 values for the inhibition of specific probe substrates for CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, by ziprasidone, risperidone and 9-hydroxyrisperidone were also detd. using human liver microsomes from three subjects. Mean Ki values were calcd. Results Three CYP-mediated metabolites - ziprasidone sulfoxide, **ziprasidone sulfone** and oxindole acetic acid-were identified. The apparent Km and Vmax values for the formation of the major metabolite, ziprasidone sulfoxide (measured as the sum of sulfoxide and sulfone) were 235 .mu.M and 1.14 nmol mg-1 protein min-1, resp. Isoform-selective inhibitors and recombinant enzymes indicated that CYP3A4 is responsible for the formation of ziprasidone metabolites. Ziprasidone was not a substrate for the other isoforms studied. Similar in vitro inhibition of CYP2D6 (Ki 6.9-16 .mu.M) and CYP3A4 (Ki 64-80 .mu.M) was obtained with ziprasidone, risperidone and 9-hydroxyrisperidone. The in vivo free drug concns. assocd. with clin. EDs of ziprasidone are at least 1500-fold lower than the mean Ki for either CYP2D6 inhibition or CYP3A4 inhibition. Conclusions Ziprasidone is predominantly metabolized by CYP3A4 in human liver microsomes and is not expected to mediate drug interactions with coadministered CYP substrates, at clin. EDs.

L2 ANSWER 3 OF 4 BIOSIS COPYRIGHT 2001 BIOSIS

AB Aims To identify the cytochrome P450 (CYP) isoform(s) responsible for the formation of the primary metabolite of ziprasidone (ziprasidone sulphoxide), to determine the kinetics of its formation and to predict possible drug interactions by investigating CYP isoform inhibition in an in vitro study. Methods In vitro metabolism of (14C)-ziprasidone was

studied using human liver microsomes. The metabolites were identified using mass spectrometry. The kinetics of metabolite formation were determined using (14C)-ziprasidone (10-200 mum) over 5 min, and Km and Vmax were estimated from Lineweaver-Burk plots. IC50 values for the inhibition of specific probe substrates for CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, by ziprasidone, risperidone and 9-hydroxyrisperidone were also determined using human liver microsomes from three subjects. Mean Ki values were calculated. Results Three CYP-mediated metabolites - ziprasidone sulphoxide, ziprasidone sulphone and oxindole acetic acid - were identified. The apparent Km and Vmax values for the formation of the major metabolite, ziprasidone sulphoxide (measured as the sum of sulphoxide and sulphone) were 235 mum and 1.14 nmol mg-1 protein min-1, respectively. Isoform-selective inhibitors and recombinant enzymes indicated that CYP3A4 is responsible for the formation of ziprasidone metabolites. Ziprasidone was not a substrate for the other isoforms studied. Similar in vitro inhibition of CYP2D6 (Ki 6.9-16 mum) and CYP3A4 (Ki 64-80 mum) was obtained with ziprasidone, risperidone and 9-hydroxyrisperidone. The in vivo free drug concentrations associated with clinically effective doses of ziprasidone are at least 1500-fold lower than the mean Ki for either CYP2D6 inhibition or CYP3A4 inhibition. Conclusions Ziprasidone is predominantly metabolized by CYP3A4 in human liver microsomes and is not expected to mediate drug interactions with coadministered CYP substrates, at clinically effective doses.

L2 ANSWER 4 OF 4 BIOSIS COPYRIGHT 2001 BIOSIS

AB The pharmacokinetics, metabolism, and excretion of a new anti-psychotic drug, ziprasidone, were studied in four normal male volunteers after oral administration of a single 20 mg dose of a mixture of 14C- and 3H-labeled ziprasidone. Blood, urine, and feces were collected at various intervals for determination of total radioactivity and metabolic profiles. Eleven days after the dose, 20.3 +- 1% of the administered radioactivity was recovered in the urine and 66.3 +- 4.8% in feces. The absorption of ziprasidone was rapid, and the C-max for ziprasidone and metabolites occurred at 2 to 6 hr postdose. Mean peak serum concentration of unchanged drug was 45 ng/ml and a mean AUC-(o-t) of 335.7 ng cntdot hr/ml. Mean peak serum concentration of total radioactivity (average of 3H and 14C) was 91 ng-eq/ml and a mean AUC-(o-t) of 724.6 ng-eq cntdot hr/ml. On the basis of AUC-(o-t) values, apprx 46% of circulating radioactivity was attributable to unchanged drug. Ziprasidone was extensively metabolized and only a small amount (lt 5% of the administered dose) was excreted in urine and feces as unchanged drug. Twelve metabolites in human urine and serum were identified by ion-spray LC/MS and LC/MS/MS with simultaneous monitoring of radioactivity. The major urinary metabolites were identified as oxindole-acetic acid and its glucuronide conjugate, benzisothiazole-3-yl-piperazine (BITP), BITP-sulfoxide, BITP-sulfone and its lactam, ziprasidone-sulfoxide, and sulfone similar to those identified in rats. In addition, two novel metabolic pathways (reductive cleavage and N-dearylation of the benzisothiazole ring) were identified for ziprasidone in humans. The metabolites resulted by these pathways were characterized as S-methyl-dihydroziprasidone, S-methyl-dihydro-ziprasidone sulfoxide, and 6-chloro-5-(2-piperazin-1-yl-ethyl-1,3-dihydro-indol-2-one, respectively. Ziprasidone suffoxide and sulfone were the major metabolites

in human serum. The affinities of the sulfoxide and sulfone metabolites for 5-HT-2 and D-2 receptors are low with respect to ziprasidone, and are thus unlikely to contribute to its antipsychotic effects. Structures of the major metabolites were confirmed by chromatographic and spectroscopic comparisons to synthetic standards. Based on the structures of these metabolites, four routes of metabolism of ziprasidone were identified: 1) N-dealkylation of the ethyl side chain attached to the piperazinyl nitrogen, 2) oxidation at sulfur resulting in the formation of sulfoxide and sulfone, 3) reductive cleavage of the benzisothiazole moiety, and 4) hydration of the C dbd N bond and subsequent suffer oxidation or N-dearylation of the benzisothiazole moiety. The identified metabolites accounted for gt 90% of total radioactivity recovered in urine.

=> d 4 all

L2 ANSWER 4 OF 4 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:397763 BIOSIS
DN PREV199799696966
TI Metabolism and excretion of a new antipsychotic drug, ziprasidone, in humans.
AU Prakash, Chandra (1); Kamel, Amin; Gummerus, Judith; Wilner, Keith
CS (1) Dep. Drug Metabolism, Central Res. Div., Pfizer Inc., Groton, CT 06340
USA
SO Drug Metabolism and Disposition, (1997) Vol. 25, No. 7, pp. 863-872. ISSN: 0090-9556.
DT Article
LA English
AB The pharmacokinetics, metabolism, and excretion of a new anti-psychotic drug, ziprasidone, were studied in four normal male volunteers after oral administration of a single 20 mg dose of a mixture of 14C- and 3H-labeled ziprasidone. Blood, urine, and feces were collected at various intervals for determination of total radioactivity and metabolic profiles. Eleven days after the dose, 20.3 +- 1% of the administered radioactivity was recovered in the urine and 66.3 +- 4.8% in feces. The absorption of ziprasidone was rapid, and the C-max for ziprasidone and metabolites occurred at 2 to 6 hr postdose. Mean peak serum concentration of unchanged drug was 45 ng/ml and a mean AUC-(o-t) of 335.7 ng cntdot hr/ml. Mean peak serum concentration of total radioactivity (average of 3H and 14C) was 91 ng-eq/ml and a mean AUC-(o-t) of 724.6 ng-eq cntdot hr/ml. On the basis of AUC-(o-t) values, apprx 46% of circulating radioactivity was attributable to unchanged drug. Ziprasidone was extensively metabolized and only a small amount (lt 5% of the administered dose) was excreted in urine and feces as unchanged drug. Twelve metabolites in human urine and serum were identified by ion-spray LC/MS and LC/MS/MS with simultaneous monitoring of radioactivity. The major urinary metabolites were identified as oxindole-acetic acid and its glucuronide conjugate, benzisothiazole-3-yl-piperazine (BITP), BITP-sulfoxide, BITP-sulfone and its lactam, ziprasidone-sulfoxide, and sulfone similar to those identified in rats. In addition, two novel metabolic pathways (reductive cleavage and N-dearylation of the benzisothiazole ring) were identified for ziprasidone in humans. The metabolites resulted by these pathways were characterized as S-methyl-dihydroziprasidone, S-methyl-dihydro-ziprasidone sulfoxide,

and 6-chloro-5-(2-piperazin-1-yl-ethyl-1,3-dihydro-indol-2-one, respectively. Ziprasidone suffoxide and sulfone were the major metabolites
in human serum. The affinities of the sulfoxide and sulfone metabolites for 5-HT-2 and D-2 receptors are low with respect to ziprasidone, and are thus unlikely to contribute to its antipsychotic effects. Structures of the major metabolites were confirmed by chromatographic and spectroscopic comparisons to synthetic standards. Based on the structures of these metabolites, four routes of metabolism of ziprasidone were identified: 1) N-dealkylation of the ethyl side chain attached to the piperazinyl nitrogen, 2) oxidation at sulfur resulting in the formation of sulfoxide and sulfone, 3) reductive cleavage of the benzisothiazole moiety, and 4) hydration of the C dbd N bond and subsequent suffer oxidation or N-dearylation of the benzisothiazole moiety. The identified metabolites accounted for gt 90% of total radioactivity recovered in urine.

CC Biochemical Methods - General *10050
Biochemical Studies - General *10060
Biophysics - General Biophysical Techniques *10504
Metabolism - General Metabolism; Metabolic Pathways *13002
Digestive System - Physiology and Biochemistry *14004
Blood, Blood-Forming Organs and Body Fluids - Blood and Lymph Studies *15002
Urinary System and External Secretions - Physiology and Biochemistry *15504
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Neuropharmacology *22024
Pharmacology - Psychopharmacology *22026

BC Hominidae *86215

IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Digestive System (Ingestion and Assimilation); Metabolism; Methods and Techniques; Pharmacology; Urinary System (Chemical Coordination and Homeostasis)

IT Chemicals & Biochemicals
ZIPRASIDONE

IT Miscellaneous Descriptors
ANALYTICAL METHOD; ANTIPSYCHOTIC-DRUG; DRUG METABOLISM; FECES; ION-SPRAY LIQUID CHROMATOGRAPHY/MASS SPECTROMETRY; MALE; METABOLITE; PHARMACOKINETICS; PHARMACOLOGY; SERUM; URINE; ZIPRASIDONE; **ZIPRASIDONE SULFONE**; ZIPRASIDONE SULFOXIDE

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
human (Hominidae)

ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

RN 146939-27-7 (ZIPRASIDONE)

=> s ziprasidone sulfoxide or 188797-80-0/rn
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
L3 8 ZIPRASIDONE SULFOXIDE OR 188797-80-0/RN

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4 5 DUP REM L3 (3 DUPLICATES REMOVED)

=> d l4 1-5 ab kwic bib

L4 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2001 ACS

AB The invention relates to novel methods using, and pharmaceutical compns. comprising ziprasidone metabolites. The methods and compns. of the invention are suitable for the treatment of neuroleptic and related disorders. **Ziprasidone sulfoxide** and ziprasidone sulfone are prepd., their 5-HT2 and dopamine D2 receptor activity studied, and dosage forms contg. the compds. are presented.

AB . . . comprising ziprasidone metabolites. The methods and compns. of the invention are suitable for the treatment of neuroleptic and related disorders. **Ziprasidone sulfoxide** and ziprasidone sulfone are prepd., their 5-HT2 and dopamine D2 receptor activity studied, and dosage forms contg. the compds. are. . .

IT 188797-77-5P, Ziprasidone sulfone **188797-80-0P, Ziprasidone sulfoxide**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(ziprasidone metabolite compns. for the treatment of neuroleptic and related disorders)

AN 2000:725450 CAPLUS

DN 133:276365

TI Ziprasidone metabolite compositions for the treatment of neuroleptic and related disorders

IN Barberich, Timothy J.; Rubin, Paul D.; Yelle, William E.

PA Sepracor Inc., USA

SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000059489	A2	20001012	WO 2000-US8707	20000331
	WO 2000059489	A3	20010525		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-127939 P 19990406

L4 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2001 ACS

AB The aim of this study was to identify the cytochrome P 450 (CYP) isoform(s) responsible for the formation of the primary metabolite of ziprasidone (**ziprasidone sulfoxide**), to det. the kinetics of its formation and to predict possible drug interactions by investigating CYP isoform inhibition in an in vitro study. Methods In vitro metab. of [14C]-ziprasidone was studied using human liver microsomes. The metabolites were identified using mass spectrometry. The kinetics of metabolite formation were detd. using [14C]-ziprasidone (10-200 .mu.M) over 5 min, and Km and Vmax were estd. from Lineweaver-Burk

plots. IC50 values for the inhibition of specific probe substrates for CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, by ziprasidone, risperidone and 9-hydroxyrisperidone were also detd. using human liver microsomes from three subjects. Mean Ki values were calcd. Results Three CYP-mediated metabolites - **ziprasidone sulfoxide**, ziprasidone sulfone and oxindole acetic acid-were identified. The apparent Km and Vmax values for the formation of the major metabolite, **ziprasidone sulfoxide** (measured as the sum of sulfoxide and sulfone) were 235 .mu.M and 1.14 nmol mg-1 protein min-1, resp. Isoform-selective inhibitors and recombinant enzymes indicated that CYP3A4 is responsible for the formation of ziprasidone metabolites. Ziprasidone was not a substrate for the other isoforms studied. Similar in vitro inhibition of CYP2D6 (Ki 6.9-16 .mu.M) and CYP3A4 (Ki 64-80 .mu.M) was obtained with ziprasidone, risperidone and 9-hydroxyrisperidone. The in vivo free drug concns. assocd. with clin. EDs of ziprasidone are at least 1500-fold lower than the mean Ki for either CYP2D6 inhibition or CYP3A4 inhibition. Conclusions Ziprasidone is predominantly metabolized by CYP3A4 in human liver microsomes and is not expected to mediate drug interactions with coadministered CYP substrates, at clin. EDs.

AB . . . study was to identify the cytochrome P 450 (CYP) isoform(s) responsible for the formation of the primary metabolite of ziprasidone (**ziprasidone sulfoxide**), to det. the kinetics of its formation and to predict possible drug interactions by investigating CYP isoform inhibition in an. . . were also detd. using human liver microsomes from three subjects. Mean Ki values were calcd. Results Three CYP-mediated metabolites - **ziprasidone sulfoxide**, ziprasidone sulfone and oxindole acetic acid-were identified. The apparent Km and Vmax values for the formation of the major metabolite, **ziprasidone sulfoxide** (measured as the sum of sulfoxide and sulfone) were 235 .mu.M and 1.14 nmol mg-1 protein min-1, resp. Isoform-selective inhibitors. . .

IT 9035-51-2, Cytochrome P 450, biological studies 87691-87-0 188797-77-5
188797-78-6 **188797-80-0**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(identification of human liver cytochrome P 450 isoform(s) responsible for formation of primary metabolites of ziprasidone and prediction of possible drug interactions)

AN 2000:263306 CAPLUS

DN 133:68333

TI Identification of the major human liver cytochrome P450 isoform(s) responsible for the formation of the primary metabolites of ziprasidone and prediction of possible drug interactions

AU Prakash, C.; Kamel, A.; Cui, D.; Whalen, R. D.; Miceli, J. J.; Tweedie, D.

CS Department of Drug Metabolism, Pfizer Central Research, Groton, CT, 06340, USA

SO Br. J. Clin. Pharmacol. (2000), 49(Suppl. 1), 35S-42S
CODEN: BCPHBM; ISSN: 0306-5251

PB Blackwell Science Ltd.

DT Journal

LA English

RE.CNT 30

RE

(4) Howard, H; J Labelled Compd Radiopharm 1994, V34, P117 CAPLUS
(7) Kronbach, T; Meth Enzymol 1991, V206, P509 CAPLUS

(8) Meier, U; Anal Biochem 1985, V151, P286 CAPLUS
(10) Nelson, D; DNA Cell Biol 1993, V12, P1 CAPLUS
(11) Newton, D; Drug Metab Dispos 1995, V23, P154 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 5 BIOSIS COPYRIGHT 2001 BIOSIS
AB Aims To identify the cytochrome P450 (CYP) isoform(s) responsible for the formation of the primary metabolite of ziprasidone (ziprasidone sulphoxide), to determine the kinetics of its formation and to predict possible drug interactions by investigating CYP isoform inhibition in an in vitro study. Methods In vitro metabolism of (14C)-ziprasidone was studied using human liver microsomes. The metabolites were identified using mass spectrometry. The kinetics of metabolite formation were determined using (14C)-ziprasidone (10-200 mum) over 5 min, and Km and Vmax were estimated from Lineweaver-Burk plots. IC50 values for the inhibition of specific probe substrates for CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, by ziprasidone, risperidone and 9-hydroxyrisperidone were also determined using human liver microsomes from three subjects. Mean Ki values were calculated. Results Three CYP-mediated metabolites - ziprasidone sulphoxide, ziprasidone sulphone and oxindole acetic acid - were identified. The apparent Km and Vmax values for the formation of the major metabolite, ziprasidone sulphoxide (measured as the sum of sulphoxide and sulphone) were 235 mum and 1.14 nmol mg-1 protein min-1, respectively. Isoform-selective inhibitors and recombinant enzymes indicated that CYP3A4 is responsible for the formation of ziprasidone metabolites. Ziprasidone was not a substrate for the other isoforms studied. Similar in vitro inhibition of CYP2D6 (Ki 6.9-16 mum) and CYP3A4 (Ki 64-80 mum) was obtained with ziprasidone, risperidone and 9-hydroxyrisperidone. The in vivo free drug concentrations associated with
clinically effective doses of ziprasidone are at least 1500-fold lower than the mean Ki for either CYP2D6 inhibition or CYP3A4 inhibition. Conclusions Ziprasidone is predominantly metabolized by CYP3A4 in human liver microsomes and is not expected to mediate drug interactions with coadministered CYP substrates, at clinically effective doses.
IT . . .
cytochrome P450; oxindole acetic acid; risperidone: antipsychotic - drug; ziprasidone: adverse effects, antipsychotic - drug, dosage, metabolism, metabolite; ziprasidone sulfone; **ziprasidone sulfoxide**: formation
AN 2000:235113 BIOSIS
DN PREV200000235113
TI Identification of the major human liver cytochrome P450 isoform(s) responsible for the formation of the primary metabolites of ziprasidone and prediction of possible drug interactions.
AU Prakash, C. (1); Kamel, A.; Cui, D.; Whalen, R. D.; Miceli, J. J.; Tweedie, D.
CS (1) Department of Drug Metabolism, Pfizer Central Research Division, Groton, CT, 06340 USA
SO British Journal of Clinical Pharmacology, (2000) Vol. 49, No. Suppl. 1, pp. 35S-42S.
ISSN: 0306-5251.
DT Article
LA English
SL English

L4 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1
AB The pharmacokinetics, metab., and excretion of a new antipsychotic drug, ziprasidone, were studied in four normal male volunteers after oral administration of a single 20 mg dose of a mixt. of 14C- and 3H-labeled

ziprasidone. Blood, urine, and feces were collected at various intervals for detn. of total radioactivity and metabolic profiles. Eleven days after the dose, 20.3.+-.1% of the administered radioactivity was recovered in the urine and 66.3.+-.4.8% in feces. The absorption of ziprasidone was rapid, and the Cmax for ziprasidone and metabolites occurred at 2 to 6 h postdose. Mean peak serum concn. of unchanged drug was 45 ng/mL and a mean AUC(o-t) of 335.7 ng .cntdot. hr/mL. Mean peak serum concn. of total radioactivity (av. of 3H and 14C) was 91 ng-eq/mL and a mean AUC(o-t) of 724.6 ng-eq .cntdot. hr/mL. On the basis of AUC(o-t) values, .apprx.46% of circulating radioactivity was attributable to unchanged drug. Ziprasidone was extensively metabolized and only a small amt. (<5% of the administered dose) was excreted in urine and feces as unchanged drug. Twelve metabolites in human urine and serum were identified by ion-spray LC/MS and LC/MS/MS with simultaneous monitoring of radioactivity. The major urinary metabolites were identified as oxindole-acetic acid and its glucuronide conjugate, benzisothiazole-3-yl-piperazine (BITP), BITP-sulfoxide, BITP-sulfone and its lactam, **ziprasidone-sulfoxide**, and sulfone similar to those identified in rats. In addn., two novel metabolic pathways (reductive cleavage and N-dearylation of the benzisothiazole ring) were identified for ziprasidone in humans. The metabolites resulted by these pathways were characterized as S-methyl-dihydro-ziprasidone, S-methyl-dihydro-**ziprasidone sulfoxide**, and 6-chloro-5-(2-piperazin-1-yl-ethyl)-1,3-dihydro-indol-2-one, resp. **Ziprasidone sulfoxide** and sulfone were the major metabolites in human serum. The affinities of the sulfoxide and sulfone metabolites for 5-HT2 and D2 receptors are low with respect to ziprasidone, and are thus unlikely to contribute to its antipsychotic effects. Structures of the major metabolites were confirmed by chromatog. and spectroscopic comparisons to synthetic stds. Based on the structures of these metabolites, four routes of metab. of ziprasidone were identified: (1) N-dealkylation of the Et side chain attached to the piperazinyl nitrogen, (2) oxidn. at sulfur resulting in the formation of sulfoxide and sulfone, (3) reductive cleavage of the benzisothiazole moiety, and (4) hydration of the C=N bond and subsequent sulfur oxidn. or N-dearylation of the benzisothiazole moiety. The identified metabolites accounted for >90% of total radioactivity recovered in urine.

AB . . . The major urinary metabolites were identified as oxindole-acetic acid and its glucuronide conjugate, benzisothiazole-3-yl-piperazine (BITP), BITP-sulfoxide, BITP-sulfone and its lactam, **ziprasidone-sulfoxide**, and sulfone similar to those identified in rats. In addn., two novel metabolic pathways (reductive cleavage and N-dearylation of the benzisothiazole ring) were identified for ziprasidone in humans. The metabolites resulted by these pathways were characterized as S-methyl-dihydro-ziprasidone, S-methyl-dihydro-**ziprasidone sulfoxide**, and 6-chloro-5-(2-piperazin-1-yl-ethyl)-1,3-dihydro-indol-2-one, resp. **Ziprasidone sulfoxide** and sulfone were the major metabolites in human serum. The affinities of the sulfoxide and sulfone metabolites for 5-HT2 and. . .

IT 87691-87-0 128396-56-5 131540-88-0 131779-40-3 188797-74-2
188797-77-5 188797-78-6 188797-79-7 **188797-80-0**
194280-90-5 194280-91-6 194350-81-7
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(metab. and excretion of a new antipsychotic drug, ziprasidone, in humans)

AN 1997:494386 CAPLUS

DN 127:185322
TI Metabolism and excretion of a new antipsychotic drug, ziprasidone, in humans
AU Prakash, Chandra; Kamel, Amin; Gummerus, Judith; Wilner, Keith
CS Central Research Division, Departments of Drug Metabolism, Pfizer, Inc., Groton, CT, 06340, USA
SO Drug Metab. Dispos. (1997), 25(7), 863-872
CODEN: DMDSAI; ISSN: 0090-9556
PB Williams & Wilkins
DT Journal
LA English

L4 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2001 ACS
AB The metab. and excretion of ziprasidone (5-[2-{4-(1,2-benzisothiazol-3-yl)piperazin-1-yl}-6-chloroindolin-2-one] hydrochloride hydrate) were studied in Long Evans rats after oral administration of a single dose of a mixt. of 14C- and 3H-labeled ziprasidone. The radioactive dose was quant. recovered over 7 days in both male and female rats. The percentage of the dose excreted in urine, bile, and feces of rats was 21.6, 19.2, and 55.6%, resp. The total excretion in urine and bile suggested that at least 41% of the drug was absorbed. Absorption of ziprasidone was rapid, and the mean plasma concns. of the unchanged drug and metabolites were slightly higher in the female rats than in the males. The maximal plasma concns. for ziprasidone and metabolites were reached at 1 h in both male and female rats. Based on AUC (0-12 h) values, approx. 59 and 52% of the circulating radioactivity (av. of 14C and 3H) was attributable to metabolites in male and female rats, resp. Ziprasidone was extensively metabolized in rats, and only a small amt. of ziprasidone was excreted as unchanged drug. Twelve metabolites were identified by ion spray LC/MS, using a combination of parent ion and product ion scanning techniques. The structures of eight metabolites were unambiguously confirmed by coelution on HPLC with synthetic stds., and four addnl. metabolites were partially identified. There was a gender-related difference in the excretion of urinary metabolites in Long Evans rats. The major route of metab. in male rats involved N-dealkylation. In female rats the major metabolites were due to oxidn. at the benzisothiazole ring. Based on the structures of these metabolites, four major and two minor routes of metab. of ziprasidone were identified. The major routes included (1) N-dealkylation of the Et side chain attached to the piperazinyl nitrogen, (2) oxidn. at the sulfur resulting in the formation of sulfoxide and sulfone, (3) oxidn. on the benzisothiazole moiety (other than sulfur), (4) hydration of the C=N bond and subsequent oxidn. at the sulfur of the benzisothiazole moiety. The minor routes involved N-oxidn. on the piperazine ring and hydrolysis of the oxindole moiety.
IT 87691-87-0 128396-56-5 131540-88-0 **188797-80-0**
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(metab. and excretion of antipsychotic drug ziprasidone in rats after oral administration of mixt. of 14C- and 3H-labeled drug)
AN 1997:165727 CAPLUS
DN 126:258418
TI Metabolism and excretion of the novel antipsychotic drug ziprasidone in rats after oral administration of a mixture of 14C- and 3H-labeled ziprasidone

AU Prakash, Chandra; Kamel, Amin; Anderson, Wayne; Howard, Harry
CS Deps. Drug Metabolism and Medicinal Chem., Pfizer Inc., Groton, CT, 06340,
USA
SO Drug Metab. Dispos. (1997), 25(2), 206-218
CODEN: DMDSAI; ISSN: 0090-9556
PB Williams & Wilkins
DT Journal
LA English

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FULL ESTIMATED COST	0.15	0.15

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CA INDEXING COPYRIGHT (C) 2001 AMERICAN CHEMICAL SOCIETY (ACS)

=> s estrogen
L1 292294 ESTROGEN

=> s multivitamin
L2 4406 MULTIVITAMIN

=> s l1 and l2
L3 63 L1 AND L2

=> s l3 and py<2000
2 FILES SEARCHED...
4 FILES SEARCHED...
L4 51 L3 AND PY<2000

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5 46 DUP REM L4 (5 DUPLICATES REMOVED)

=> d 15 1-5 ab

L5 ANSWER 1 OF 46 USPATFULL
AB The present invention pertains generally to the field of Public Health, including the prevention and treatment of coronary heart disease which is currently the first cause of death in the American population. More specifically, the present invention concerns a total modular system of **multivitamin** and mineral supplementation composed of 7 distinct modules for improving public health by insuring adequate intake of micronutrients needed for disease prevention and protection against nutritional losses and deficiencies due to, for example, lifestyle factors and common inadequate dietary patterns. A module, as used herein throughout, is defined as a separate and distinct combination of vitamin-mineral and other health promoting compounds which are directed to specific target populations. The formulations of the present invention which, when combined in one capsule or tablet or as separate modules, exert a joint and enhancing effect on the major pathogenetic factors involved in the atherosclerotic process. Moreover, certain modular formulations of the present invention incorporate both antioxidants and acetylsalicylic acid (aspirin) as a single preventive modality. Such a combination of antioxidants and aspirin is believed to act to prevent oxidation of low density lipoproteins within coronary arterial walls and to cause platelet deagluttination thereby inhibiting thrombus formation. The benefit of preventing these two major processes is believed to reduce the risk of coronary heart disease.

L5 ANSWER 2 OF 46 USPATFULL
AB The present invention pertains generally to the field of Public Health, including the prevention and treatment of coronary heart disease which is currently the first cause of death in the American population. More

specifically, the present invention concerns a total modular system of **multivitamin** and mineral supplementation composed of 7 distinct modules for improving public health by insuring adequate intake of micronutrients needed for disease prevention and protection against nutritional losses and deficiencies due to, for example, lifestyle factors and common inadequate dietary patterns. A module, as used herein throughout, is defined as a separate and distinct combination of vitamin-mineral and other health promoting compounds which are directed to specific target populations. The formulations of the present invention which, when combined in one capsule or tablet or as separate modules, exert a joint and enhancing effect on the major pathogenetic factors involved in the atherosclerotic process. Moreover, certain modular formulations of the present invention incorporate both antioxidants and acetylsalicylic acid (aspirin) as a single preventive modality. Such a combination of antioxidants and aspirin is believed to act to prevent oxidation of low density lipoproteins within coronary arterial walls and to cause platelet deagluttination thereby inhibiting thrombus formation. The benefit of preventing these two major processes is believed to reduce the risk of coronary heart disease.

L5 ANSWER 3 OF 46 USPATFULL

AB The present invention provides methods for treating physical conditions resulting from postmenopausal **estrogen** decline in a postmenopausal subject, and in particular methods for reducing the risk of osteoporotic bone fractures in a postmenopausal subject. The present invention also provides a kit useful for carrying out the methods of the present invention.

L5 ANSWER 4 OF 46 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

L5 ANSWER 5 OF 46 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1

AB In the following, the authors examine the relationship between hormonal climate and the female voice through discussion of hormonal biochemistry and physiology and informal reporting on a study of 197 women with either premenstrual or menopausal voice syndrome. These facts are placed in a larger historical and cultural context, which is inextricably bound to the understanding of the female voice. The female voice evolves from childhood to menopause, under the varied influences of **estrogens**, progesterone, and testosterone. These hormones are the dominant factor in determining voice changes throughout life. For example, a woman's voice always develops masculine characteristics after an injection of testosterone such a change is irreversible. Conversely, male castrati had feminine voices because they lacked the physiologic changes associated with testosterone. The vocal instrument is comprised of the vibratory body, the respiratory power source and the oropharyngeal resonating chambers. Voice is characterized by its intensity, frequency, and harmonics. The harmonics are hormonally dependent. This is illustrated by the changes that occur during male and female puberty. In the female, the impact of **estrogens** at puberty, in concert with progesterone, produces the characteristics of the female voice, with a fundamental frequency one third lower than that of a child. In the male, androgens released at puberty are responsible for the male vocal frequency, an octave lower than that of a child. Premenstrual vocal syndrome is characterized by vocal fatigue, decreased range, a loss of power and loss of certain harmonics. The syndrome usually starts some 4-5 days before menstruation in some 33% of women. Vocal professionals are particularly

affected. Dynamic vocal exploration by televideoendoscopy shows congestion, microvarices, edema of the posterior third of the vocal folds and a loss of its vibratory amplitude. The authors studied 97 premenstrual women who were prescribed a treatment of **multivitamins**, venous tone stimulants (phlebotonics), and anti-edematous drugs. We obtained symptomatic improvement in 84 patients. The menopausal vocal syndrome is characterized by lowered vocal intensity, vocal fatigue, a decreased range with loss of the high tones and a loss of vocal quality. In a study of 100 menopausal women, 17 presented with a menopausal vocal syndrome. To rehabilitate their voices, and thus their professional lives, patients were prescribed hormone replacement therapy and multi-vitamins. All 97 women showed signs of vocal muscle atrophy, reduction in the thickness of the mucosa and reduced mobility in the cricoarytenoid joint. Multi-factorial therapy (hormone replacement therapy and multi-vitamins) has to be individually adjusted to each case depending on body type, vocal needs, and other factors.

=> d 2-3 kwic

L5 ANSWER 2 OF 46 USPATFULL
PI US 5948443 19990907 <--
AB . . . the first cause of death in the American population. More specifically, the present invention concerns a total modular system of **multivitamin** and mineral supplementation composed of 7 distinct modules for improving public health by insuring adequate intake of micronutrients needed for. . .
SUMM The present invention concerns a total modular system of **multivitamin** and mineral supplementation composed of 7 distinct modules for improving public health by insuring adequate intake of micronutrients needed for. . .
SUMM . . . many of the attendant advantages thereof, the following detailed description and examples are given concerning the novel modular systems of **multivitamin** and mineral supplementation of the present invention.
SUMM As indicated above, the present invention concerns a total modular system of **multivitamin** and mineral supplementation composed of 7 distinct modules for insuring adequate intake of micronutrients needed for disease prevention and protection. . .
SUMM . . . Module 1 formulation takes into account higher levels of antioxidant nutrients and other geroprotective nutrients than is found in ordinary **multivitamin**-vitamin preparations.
SUMM . . . Reviews Vol. 51, No. 4 April 1993 PP 106-115. Risk of infection in the elderly was also decreased when a **multivitamin** preparation was taken daily. See Chandra, R. K. Effect of Vitamin and Trace-element Supplementation on Immune Responses and Infection in. . .
SUMM . . . for neutrophil locomotory dysfunction in blunt trauma. J. of Trauma, 31(8):1142-50, August 1991, Verix Vitamin E Information Service. Post-operative oral **multivitamin** supplementation in a study of 140 patients also was found to be useful in correcting folate and B12 anemias following gastric bypass surgery. See Brolin, R E., Gorman, R.

C., Milgrim, L. M., Kenler, H. A. **Multivitamin** prophylaxis in prevention of post-gastric bypass vitamin and mineral deficiencies. Inter. J of Obesity, 15(10):661-7, October 1991. Burned patients exhibit. . .

SUMM . . . age 65 and over. For women especially, this may increase their risk of developing osteoporosis due in part to decreased **estrogen** levels as they increase in age. The Module 1 formula for men or women provides over 500 mg of calcium. . . individual consuming two servings of milk products daily could have a sufficient intake. However, post-menopausal women who are not taking **estrogen**, and those who have had hysterectomies may require higher intakes of calcium. An additional 450 mg of calcium is provided. . .

SUMM In accordance with Module 4, this novel **multivitamin**, mineral and antioxidant formulation is specifically designed to include aspirin, or plants rich in salicylic acid such as willow bark. . .

SUMM . . . use of aspirin by selected persons on a daily basis as a preventive agent. Many of these consumers also take **multivitamins** which may interfere with aspirin's benefits. For example, many **multivitamin** preparations contain vitamin K. One popular brand is designed for older individuals and contains 80 mcg of vitamin K. This. . .

SUMM The presence of certain compounds, such as vitamin K, in commonly sold **multivitamin** formulations may negate the full benefits of aspirin for some individuals. Recent data suggest that aspirin significantly delays and inhibits. . .

DETD Anti-platelet agglutinating response of aspirin given at the same time with a Module 1 **multivitamin** and mineral formulation is studied.

DETD . . . consists of 2 females (one smoker) and 1 male who also take 81 mg of aspirin with a commercially available **multivitamin** (with 80 mcg of vitamin K) plus 81 mg of aspirin. One nonsmoker increases her bleeding time to over 15. . .

CLM What is claimed is:

. . . of coronary heart disease said method comprising: administering concomitantly to a human on a daily basis an effective amount of **multivitamins** and minerals and an effective amount of acetylsalicylic acid, wherein the effective amount of **multivitamins** and minerals comprises:

Vitamin B-1	about 0.7 to about 15 mg
Vitamin B2	about 0.7 to about 15 mg
Vitamin B6. . .	

L5 ANSWER 3 OF 46 USPATFULL

TI Methods for treating postmenopausal women using ultra-low doses of **estrogen**

PI US 5891868 19990406 <--

AB The present invention provides methods for treating physical conditions resulting from postmenopausal **estrogen** decline in a postmenopausal subject, and in particular methods for reducing the risk of osteoporotic bone fractures in a postmenopausal. . .

SUMM Endogenous **estrogens** fall dramatically after natural or surgical menopause, and this decline results in a marked increase in bone loss and subsequent fractures. Endogenous **estrogens** are clearly important for the maintenance of skeletal health in younger women. However, the importance of endogenous **estrogens** in older women is less certain.

SUMM . . . fractures. S. R. Cummings, et al., J. Bone Min. Res. 10 (Suppl

I):S174 (1995). However, estradiol is a more potent **estrogen** that estrone, and studies of its relationship to fractures have been inconclusive. Serum estradiol levels in premenopausal women average over. . . levels which are undetectable by conventional, sensitive assay methods (i.e., less than 5 pg/ml). Conventional treatment for postmenopausal women includes **estrogen** replacement therapy in doses sufficient to maintain serum estradiol levels above 40-60 pg/ml.

SUMM Conventional hormone replacement therapy has proven useful for treating physical conditions resulting from postmenopausal **estrogen** decline, including reducing the loss of, or even increasing bone density; and decreasing the risk of bone fracture. However, studies. . . uterus. Accordingly, there remains a need in the art for methods of treating the physical conditions which result from postmenopausal **estrogen** decline or deficiency. There also remains a need in the art for treating such physical conditions while reducing the side. .

.

SUMM As a first aspect, the present invention provides a method for treating physical conditions resulting from **estrogen** decline in a postmenopausal subject. The method comprises administering to the subject, an amount of **estrogen** which is effective to produce a serum estradiol level of between about 5 pg/ml and about 15 pg/ml.

SUMM . . . in a subject afflicted with or susceptible to postmenopausal osteoporosis. The method comprises administering to the subject, an amount of **estrogen** which is effective to produce a serum estradiol level of between about 5 pg/ml and about 15 pg/ml.

SUMM . . . present invention provides a kit for use by a consumer afflicted with or susceptible to physical conditions resulting from postmenopausal **estrogen** decline. The kit comprises a) a transdermal patch capable of transdermally administering less than about

20 .mu.g of **estrogen** per day; and b) instructions describing a method of using the transdermal patch to reduce the risk of bone fracture. . .

SUMM As a fourth aspect, the present invention provides another method for treating physical conditions resulting from postmenopausal **estrogen** decline in a postmenopausal subject. The method includes administering less than about 20 .mu.g of **estrogen** per day in the absence of exogenous progestin.

SUMM . . . fractures in a subject afflicted with or susceptible to osteoporosis. The method includes administering less than about 20 .mu.g

of **estrogen** per day in the absence of exogenous progestin.

DETD "Physical conditions resulting from postmenopausal **estrogen** decline" refers to physical conditions which are common among postmenopausal women and which are caused, at least in part, by a decline in **estrogen** in the body. These conditions include but are not limited to osteoporosis, headaches, nausea, depression, hot flashes, decrease in bone. . .

DETD . . . or other site, or who have experienced either vertebral or hip fracture. Subjects susceptible to physical conditions resulting from postmenopausal **estrogen** decline include women approaching the onset of menopause who are exhibiting a decrease in serum estradiol levels as compared to. . . who are exhibiting a decrease in serum estradiol levels but who have not yet exhibited physical conditions caused by postmenopausal **estrogen** decline. Subjects exhibiting decreased serum estradiol levels include subjects exhibiting a serum estradiol level at or below 20 pg/ml, including. . .

DETD . . . susceptible to postmenopausal physical conditions of the type discussed hereinabove. The methods of the present invention involve the administration of **estrogen** in an amount effective to produce

the desired serum estradiol level in the subject. As used herein, the phrase "treating. . . also preventing the occurrence of postmenopausal physical conditions in a subject susceptible to such conditions as a result of postmenopausal **estrogen** decline. Although treatment of these postmenopausal physical conditions may include the complete elimination of such conditions in a subject afflicted. . . the term which is contemplated by the instant invention. Thus, the present invention involves the use of ultra-low doses of **estrogen** for the treatment of physical conditions resulting from **estrogen** decline and for reducing the risk of osteoporotic bone fractures in a subject afflicted with or susceptible to postmenopausal osteoporosis.

DETD The present inventors have also unexpectedly discovered that the treatment of physical conditions resulting from **estrogen** decline can be affected by ultra low doses of **estrogen** without the need for administration of progestin. The administration of **estrogen**, excluding the administration of progestin has now been found by the present inventors to be effective for treatment of postmenopausal. . .

DETD The source of exogenous **estrogen** for use in the methods of the present invention may include any suitable form of **estrogen** for administration to a subject. Suitable forms of exogenous **estrogen** include both natural and synthetic compounds exhibiting estrogenic activity. Several forms of exogenous **estrogen** are commercially available. For example, suitable forms of exogenous **estrogen** include but are not limited to estradiols, including .alpha.-estradiol, 17.beta.-estradiol, ethinyl estradiol, estradiol benzoate, and estradiol 17.beta.-cypionate; estrone; estriol; conjugated equine **estrogens**; and salts of the forgoing. The foregoing are all examples of steroids which exhibit estrogenic activity. Examples of nonsteroidal compounds. . . estrogenic activity include but are not limited to diethylstilbestrol diphosphate, diethylstilbestrol dipropionate, and hexestrol. Currently, the preferred form of exogenous **estrogen** for use in the methods of the present invention is estradiol.

DETD The amount of exogenous **estrogen** to be administered to the subject is sufficient to achieve a serum estradiol level of at least about 5 pg/ml. . . and preferably not more than 15 pg/ml. In other words, according to the methods of the present invention, sufficient exogenous **estrogen** is administered to achieve a total serum estradiol level of at least about 5 pg/ml/ml and about 20 pg/ml. Since. . . estradiol level of an untreated subject will differ for each individual, different individuals may require administration of different doses of **estrogen** to achieve the required serum estradiol level. It is not required that the serum estradiol level of each subject being. . . treated subject must be at least about 5 and not more than about 20 pg/ml. Often, the amount of exogenous **estrogen** to be administered is sufficient to achieve a serum estradiol level of between about 5 pg/ml and about 10 pg/ml.. . . a decrease in the risk of vertebral and hip fracture. The administration of this lower than conventional amount of exogenous **estrogen** has the further advantage of decreasing the risk of undesirable side effects associated with hormone replacement therapy.

DETD The administration of exogenous **estrogen** can be accomplished by any suitable route. For example, formulations for oral and parenteral administration of exogenous **estrogen** are known in the art, and may be employed in the methods of the present invention. Formulations suitable for oral. . .

DETD The amount of exogenous **estrogen** in the oral formulation is an ultra-low dose of **estrogen** which will depend upon the precise form of **estrogen** to be administered, but is typically less than 0.5 mg per day. Preferably, the amount of **estrogen** administered orally is between about 0.1 mg and about 0.25 mg of **estrogen** per day. For example, the amount of estradiol administered orally is from about 0.1 mg to about 0.25 mg per. . . day. It is well within the skill of those in the art to determine equivalent dosages of other forms of **estrogen** as well.

DETD In the preferred embodiments of the present invention, **estrogen** is administered parenterally or transdermally rather than orally. The former routes of administration are preferred over oral administration because oral administration of **estrogen** may lead to increased levels of sex hormone binding globulin. Sex hormone binding globulin may diminish the beneficial effects of administering **estrogen** to postmenopausal subjects, particularly subjects exhibiting signs of osteoporosis or loss of bone mineral density. Although oral administration is not. . .

DETD . . . subcutaneous, intravenous, intramuscular, intradermal injection, or vaginal ring. Such preparations may conveniently be prepared by admixing the active ingredient, an **estrogen**, with water or a glycine buffer and rendering the resulting solution sterile and isotonic with the blood.

DETD The amount of exogenous **estrogen** in the parenteral formulation is an ultra-low dose of **estrogen** which will depend upon the precise form of **estrogen** to be administered, but is typically not more than 20 .mu.g per day. Preferably, the amount of **estrogen** administered parenterally is between about 5 .mu.g and about 15 .mu.g of **estrogen** per day, and more preferably about 10 .mu.g of **estrogen** per day. For example, the amount of estradiol administered parenterally is from about 5 .mu.g to about 15 .mu.g per. . . day. It is well within the skill of those in the art to determine equivalent dosages of other forms of **estrogen** as well.

DETD More preferably, the methods of the present invention include the transdermal administration of exogenous **estrogen**. Suitable formulations for the transdermal administration of **estrogen** are known in the art, and may be employed in the methods of the present invention. For example, suitable transdermal patch formulations for the administration of exogenous **estrogen** is described in U.S. Pat. No. 4,460,372 to Campbell et al., U.S. Pat. No. 4,573,996 to Kwiatek et al., U.S.. . .

DETD . . . joined to the permeable surface layer 13 at the edges of the permeable surface layer 13. The reservoir 16 contains **estrogen** and is in fluid contact with the permeable surface layer 13. The transdermal patch 10 is adhered to the skin. . . 10 is adhered to the skin. While the transdermal patch 10 is adhered to the skin of the subject, the **estrogen** contained in the reservoir 16 of the transdermal patch 10 is transferred via the permeable surface layer 13, from the. . . 10 may optionally also include one or more penetration-enhancing agents in the reservoir 16 that enhance the penetration of the **estrogen** through the skin.

DETD . . . art of transdermal patch delivery, and any conventional material which is permeable to the active ingredient to be administered, i.e., **estrogen**, may be employed in the transdermal patch of the instant invention. Specific examples of suitable materials for the permeable surface. . .

DETD . . . As will be apparent to those skilled in the art, the adhesive layer should be inert to the active ingredient, **estrogen**, and should not interfere with the transdermal delivery of the **estrogen** through the permeable surface layer. Pressure sensitive adhesives are preferred for the adhesive layer of the transdermal patch to facilitate. . .

DETD FIG. 2 is an example of second type of transdermal patch which is suitable for the transdermal delivery of **estrogen** according to the present invention. In this example, the active ingredient is incorporated in to the adhesive layer rather than. . . has the combined function of adhering the patch 20 to the skin of the subject and containing the active ingredient, **estrogen**, which is to be administered. The active ingredient is leached from the adhesive/drug layer 24 to and through the skin. . .

DETD The amount of exogenous **estrogen** in the transdermal patch formulations is an ultra-low dose of **estrogen** which will depend upon the precise form of **estrogen** to be administered, but is sufficient to deliver less than 20 .mu.g, and typically not more than 15 .mu.g per day. Preferably, the amount of **estrogen** administered via the transdermal patch is between about 5 .mu.g and about 15 .mu.g of **estrogen** per day. More preferably, the amount of **estrogen** administered is about 10 .mu.g per day. Although the typical dose of **estrogen** according to the method of the present invention is less than 20 .mu.g, doses as high as 25 .mu.g may. . . day. It is well within the skill of those in the art to determine equivalent dosages of other forms of **estrogen** as well. The ultra-low level of **estrogen** employed in the methods of the present invention has unexpectedly been found to substantially reduce the risk of osteoporotic bone. . .

DETD Typically, the transdermal patches are designed to be worn for several days before replacement is required. Thus the amount of **estrogen** in the reservoir must be sufficient to permit the administration of less than 20 .mu.g per day for a period. . . days. As an example, a transdermal patch according to the present invention which is designed to administer 10 .mu.g of **estrogen** per day for seven (7) days would contain approximately 1 mg of **estrogen**. A patch suitable for the administration of 15 .mu.g per day for seven (7) days would contain approximately 1.4 mg of **estrogen**. Based upon these specific examples, one skilled in the art would be able to discern the necessary amount of **estrogen** to be included in the transdermal patch to achieve the delivery of the correct daily dose of **estrogen**.

DETD . . . to the skin surface, for example at the upper arm, to achieve the transdermal administration of the ultra-low dose of **estrogen** from the patch and thereby increase the serum estradiol level in the consumer to between about 5 pg/ml and about. . . 20 pg/ml. The instructions would also direct the consumer to replace the patch as required to continue the administration of **estrogen** as necessary to maintain this serum estradiol level by using the transdermal patch. In particular, the instructions might direct the. . . transdermal patch every seven (7) day to ensure the administration of less than 20 .mu.g, and preferably 10 .mu.g of **estrogen** per day when a seven-day patch is utilized in the kit. Such kits could advantageously be packaged and sold in. . .

DETD . . . estradiol level and risk of osteoporotic bone fracture and also demonstrate the efficacy of using an ultra-low dose of exogenous **estrogen** to reduce the risk of osteoporotic bone fracture and

for the treatment of postmenopausal symptoms.

DETD . . . replacements or who needed the help of another person to walk. Participants were asked about current or recent use of **estrogen**, calcium supplements and **multivitamins** containing vitamin D.

DETD This example demonstrates a comparison of the effects of administering differing amounts of **estrogen** using a 7-day **estrogen** transdermal therapeutic system, on the prevention of bone loss in postmenopausal women.

DETD . . . level and loss of bone mineral density. The example also demonstrates the efficacy of using an ultra-low dose of exogenous **estrogen** to reduce loss of bone mineral density.

DETD . . . 231 and 218 women with complete calcaneal and hip BMD scan pairs, respectively, who did not report current use of **estrogen** replacement therapy during the base line interview. Sample sizes for individual assays vary due to missing values. Also, sample sizes. . .

DETD . . . baseline visit in 1986-1988, a detailed questionnaire was administered in which subjects were asked about current or previous use of **estrogen**, calcium and **multivitamins** containing vitamin D. Subjects were examined to obtain height and weight measurements.

DETD . . . for season (July-December versus January-June) and clinic, and after either adjustment for, or exclusion of, current users of calcium or **multivitamins** containing vitamin D.

DETD . . . in the lowest quartile (<21 pg/mL). This trend remained significant after adjustment for clinic, season and use of calcium and **multivitamins** containing vitamin D.

DETD The data demonstrate that lower levels of serum **estrogens** are significantly associated with increased hip bone loss in elderly women, even after controlling for age, weight and levels of. . .

DETD In conclusion, the results demonstrate that SHBG and endogenous **estrogens** are important determinants of bone loss in elderly women. Lower 25(OH)D levels are associated with more rapid bone loss from. . .

DETD . . . women for whom we did not have measures of serum estradiol (n=134) and those who reported current use of systemic **estrogen** therapy (n=39); 247 women remained available for the current analysis.

DETD . . . mellitus

	9	9	10	13	.52
Thiazide use, current	23%	15%	27%	36%	.07
Thyroid hormone use, current	7	17	11	15	.28
>10-year **estrogen** use before study	8	11	10	11	.69

DETD . . . half of the women. Estrone was not predictive of incident hip fractures. In postmenopausal women, estrone is quantitatively the predominant **estrogen** and is produced mainly from conversion of adrenal androstenedione. Estradiol is produced through reduction of estrone and through aromatization of. . .

CLM What is claimed is:

1. A method for treating physical conditions resulting from postmenopausal **estrogen** decline in a postmenopausal subject, said method comprising administering to said subject, an amount of **estrogen** which is effective to produce a serum estradiol level in said subject of between about 5 pg/ml and about 15. . .

3. The method according to claim 1 wherein said amount of **estrogen** which is administered is effective to produce a serum

estradiol level in said subject of between about 5 pg/ml and. . .
4. The method according to claim 1, comprising parenterally administering said amount of **estrogen**.

5. The method according to claim 1, comprising transdermally administering said amount of **estrogen**.

6. The method according to claim 1, comprising transdermally administering not more than about 15 .mu.g of **estrogen** per day.

7. The method according to claim 1, comprising transdermally administering between about 5 .mu.g and about 15 .mu.g of **estrogen** per day.

8. The method according to claim 1, wherein said **estrogen** is estradiol.

. . . in a subject afflicted with or susceptible to postmenopausal osteoporosis, said method comprising administering to said subject, an amount of **estrogen** which is effective to produce a serum estradiol level in said subject of between about 5 pg/ml and about 15. . .
10. The method according to claim 9, wherein said amount of **estrogen** which is administered is effective to produce a serum estradiol level in said subject of between about 5 pg/ml and. . .
11. The method according to claim 9, comprising parenterally administering said amount of **estrogen**.

12. The method according to claim 9, comprising transdermally administering said amount of **estrogen**.

13. The method according to claim 9, comprising transdermally administering not more than about 15 .mu.g of **estrogen** per day.

14. The method according to claim 9, comprising transdermally administering between about 5 .mu.g and about 15 .mu.g of **estrogen** per day.

15. The method according to claim 9, wherein said **estrogen** is estradiol.

16. A kit for use by a consumer afflicted with or susceptible to physical conditions resulting from postmenopausal **estrogen** decline, said kit comprising: a) a transdermal patch for transdermally administering less than about 15 .mu.g of **estrogen** per day; and b) instructions describing a method of using the transdermal patch to reduce the risk of osteoporotic bone. . .
17. A method for treating physical conditions resulting from postmenopausal **estrogen** decline in a postmenopausal subject, said method comprising transdermally administering less than about 20 .mu.g of **estrogen** per day to said subject, in the substantial absence of exogenous progestin.

. . . The method according to claim 17, wherein said method comprises administering between about 5 .mu.g and about 15 .mu.g of **estrogen** per day.

22. The method according to claim 17, wherein said method comprises

transdermally administering about 10 .mu.g of **estrogen** per day.

23. The method according to claim 17, wherein said **estrogen** is estradiol.

. . . in a subject afflicted with or susceptible to postmenopausal osteoporosis, said method comprising administering less than about 20 .mu.g of **estrogen** to said subject in the absence of exogenous progestin.

. . . The method according to claim 24, wherein said method comprises administering between about 5 .mu.g and about 15 .mu.g of **estrogen** per day.

28. The method according to claim 24, wherein said method comprises transdermally administering about 10 .mu.g of **estrogen** per day.

29. The method according to claim 24, wherein said **estrogen** is estradiol.

=> d 6-10 ab

L5 ANSWER 6 OF 46 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AB Background. Osteoporosis is very common in patients with end-stage pulmonary disease. However, there are few prospective data on fracture incidence after lung transplantation. Methods. We prospectively evaluated changes in bone mass, fracture incidence, and biochemical indices of bone and mineral metabolism in 30 patients who completed 1 year of observation after lung transplantation. All received calcium, vitamin D, and therapy with one or more agents that inhibit bone resorption, initiated shortly after transplantation. Results. Before transplantation, only 20% of the patients had normal lumbar spine (LS) and femoral neck bone mineral density (BMD). After transplantation, 15 patients (50%) sustained significant bone loss at either the LS (-8.6.+-.1.0%) or the femoral neck (-11.3.+-.2.2%). Eleven (37%) patients (10 women) sustained a total of 54 atraumatic fractures. Pretransplantation LS BMD and T scores were significantly lower in those who sustained fractures (-2.809.+-.0.32 versus -1.569.+-.0.29; P<0.01). Fracture patients were more likely to have had pretransplantation glucocorticoid therapy (chi-square 5.687; P<0.02). The duration of pretransplantation glucocorticoid therapy was also longer in fracture patients (4.9.+-.0.8 versus 1.3.+-.0.4 years; P<0.001). Biochemical markers of bone resorption were significantly higher in patients who sustained bone loss and/or fractures. Conclusions. We conclude that fractures are a significant problem in the first year after lung transplantation, even in patients who receive therapy to prevent bone loss. Women with low pretransplantation BMD and a history of pretransplantation glucocorticoid therapy are at greatest risk.

L5 ANSWER 7 OF 46 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AB Numerous articles and several reviews have been published on the role of antioxidants, and diet and lifestyle modifications in cancer prevention. However, the potential role of these factors in the management of human cancer have been largely ignored. Extensive in vitro studies and limited in vivo studies have revealed that individual antioxidants such as vitamin

A (retinoids), vitamin E (primarily .alpha.-tocopheryl succinate), vitamin
C (primarily sodium ascorbate) and carotenoids (primarily polar carotenoids) induce cell differentiation and growth inhibition to various degrees in rodent and human cancer cells by complex mechanisms. The proposed mechanisms for these effects include inhibition of protein kinase
C activity, prostaglandin E1-stimulated adenylate cyclase activity, expression of c- myc, H-ras, and a transcription factor (E2F), and induction of transforming growth factor-.beta. and p21 genes. Furthermore,
antioxidant vitamins individually or in combination enhance the growth-inhibitory effects of x- irradiation, chemotherapeutic agents, hyperthermia, and biological response modifiers on tumor cells, primarily in vitro. These vitamins, individually, also reduce the toxicity of several standard tumor therapeutic agents on normal cells. Low fat and high fiber diets can further enhance the efficacy of standard cancer therapeutic agents; the proposed mechanisms for these effects include the production of increased levels of butyric acid and binding of potential mutagens in the gastrointestinal tract by high fiber and reduced levels of
growth promoting agents such as prostaglandins, certain fatty acids and **estrogen** by low fat. We propose, therefore, a working hypothesis that multiple antioxidant vitamin supplements together with diet and lifestyle modifications may improve the efficacy of standard and experimental cancer therapies.

L5 ANSWER 8 OF 46 USPATFULL
AB Methods of treatment of subjects for decreasing cell mediated autoimmunity or humoral autoimmunity by administering an R'-Glu-Trp-R" pharmaceutical preparation useful in subjects having autoimmune diseases.

L5 ANSWER 9 OF 46 USPATFULL
AB Disclosed are methods for repressing reproduction of latent viruses, such as HIV, in animals by the generally concurrent administration of (1) antioxidants including a glutathione agent; and (2) an NFKB induction inhibitor. Also disclosed are pharmaceutical compositions and kits for use in repressing reproduction of latent viruses such as HIV.

L5 ANSWER 10 OF 46 USPATFULL
AB A composition and procedures for its formation and administration are described, which provide for a convenient, efficacious and simple transdermal administration of medications from a topically applied cream. No transmission through a membrane is involved. The composition incorporates at least two separate penetration enhancers which function synergistically to provide for rapid but controllable transport of the medication from the cream into the skin. The use of a plurality of penetration enhancers, at least one of which facilitates the separation of medication from the cream and at least a second of which alters the structure of the outer layers of skin, particularly the stratum corneum,
enhances migration of the drug through the stratum corneum.

=> d 11-20 ab

L5 ANSWER 11 OF 46 USPATFULL
AB A nutritional product is provided for cancer patients comprising, as per

caloric requirement, a low concentration of carbohydrate, a high concentration of fat and an imbalance of amino acids wherein L-phenylalanine, L-tyrosine and L-methionine are present in the below normal concentrations and L-leucine is present in substantial excess of normal concentrations to suppress cancer growth and as an adjunct to conventional cancer therapies.

L5 ANSWER 12 OF 46 USPATFULL
AB This invention provides methods of treating purulent inflammatory diseases by administering L-Glu-L-Trp or a salt thereof.

L5 ANSWER 13 OF 46 USPATFULL
AB Methods of treatment of subjects with systemic toxicity by administering an R'-Glu-Trp-R" pharmaceutical preparation.

L5 ANSWER 14 OF 46 USPATFULL
AB This invention provides methods for normalizing the numbers of lymphocytes in animals by administering the dipeptide L-Glu-L-Trp.

L5 ANSWER 15 OF 46 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

L5 ANSWER 16 OF 46 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AB Seizures occurred in two patients with probable Alzheimer's disease who were receiving long-term treatment with metrifonate, an irreversible acetylcholinesterase inhibitor. In both patients seizures were associated with discontinuation of short-term agents with high antimuscarinic properties. Hence, abrupt discontinuation of antimuscarinics or anticholinergics with high antimuscarinic properties in patients receiving long-term acetylcholinesterase inhibition therapy may be associated with a reduction of seizure threshold. With increasing administration of acetylcholinesterase inhibitors for patients with Alzheimer's disease, practitioners should be aware of the potential for drug-drug interactions and other complications. In general, it is good medical practice to avoid concomitant administration with centrally acting anticholinergic agents.

L5 ANSWER 17 OF 46 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

L5 ANSWER 18 OF 46 USPATFULL
AB Disclosed are methods for repressing reproduction of latent viruses, such as HIV, in animals by the generally concurrent administration of (1) antioxidants including a glutathione agent; and (2) an NFKB induction inhibitor. Also disclosed are pharmaceutical compositions and kits for use in repressing reproduction of latent viruses such as HIV.

L5 ANSWER 19 OF 46 USPATFULL
AB A pharmaceutical composition having increased bioavailability characterized by piperine of the formula ##STR1## and a drug for treating a disease or condition of the human cardiovascular system, central nervous system, gastrointestinal tract, respiratory tract, endocrine system, genito urinary tract or haemopoietic system.

L5 ANSWER 20 OF 46 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

=> s estradiol or estrogen or phytoestrogen
L6 442168 ESTRADIOL OR ESTROGEN OR PHYTOESTROGEN

```
=> s multivitamin
L7        4406 MULTIVITAMIN

=> s oral dosage form or pill or tablet or caplet
L8      218539 ORAL DOSAGE FORM OR PILL OR TABLET OR CAPLET

=> s pharmaceutical composition
L9       72907 PHARMACEUTICAL COMPOSITION

=> s l6 and l7 and l8 and l9
L10         11 L6 AND L7 AND L8 AND L9

=> d l10

L10  ANSWER 1 OF 11  USPATFULL
AN     2001:148010  USPATFULL
TI     Solid dosage form with polymeric binder
IN     Kothrade, Stephan, Limburgerhof, Germany, Federal Republic of
       Berndl, Gunther, Herxheim, Germany, Federal Republic of
       Meffert, Helmut, Mannheim, Germany, Federal Republic of
PA     BASF Aktiengesellschaft, Ludwigshafen, Germany, Federal Republic of
       (non-U.S. corporation)
PI     US 6284803          B1   20010904
AI     US 1999-395775           19990914 (9)
PRAI   DE 1998-19843904    19980924
DT     Utility
FS     GRANTED
LN.CNT 740
INCL   INCLM: 514/772.100
       INCLS: 514/772.200; 424/465.000; 424/476.000; 424/482.000
NCL    NCLM:  514/772.100
       NCLS:  514/772.200; 424/465.000; 424/476.000; 424/482.000
IC     [7]
       ICM: A61K047-30
       ICS: A61K009-20; A61K009-32; A61K009-42
EXF    514/772.1; 514/772.2; 424/465; 424/476; 424/482


=> dup rem l10
PROCESSING COMPLETED FOR L10
L11          11 DUP REM L10 (0 DUPLICATES REMOVED)

=> d l11 2-11

L11  ANSWER 2 OF 11  USPATFULL
AN     2000:105457  USPATFULL
TI     Compositions for stimulating hair growth, preventing hair loss, or
       minimizing hair loss, and methods for preparing and using same
IN     Keeney, Joseph A., Rte. 3, Box 380, Huntington, TX, United States
75949
PI     US 6103272               20000815
AI     US 1999-354290           19990715 (9)
DT     Utility
FS     Granted
LN.CNT 577
INCL   INCLM: 424/618.000
       INCLS: 424/074.000; 424/630.000
NCL    NCLM:  424/618.000
       NCLS:  424/074.000; 424/630.000
IC     [7]
```

ICM: A31K033-38
ICS: A31K007-06; A31K033-34
EXF 514/168; 424/630; 424/618; 424/401; 424/70.11; 424/450; 424/53; 424/74; 252/186.29

L11 ANSWER 3 OF 11 USPATFULL
AN 2000:74110 USPATFULL
TI Polynucleotides encoding human membrane fusion proteins
IN Hillman, Jennifer L., Mountain View, CA, United States
Lal, Preeti, Sunnyvale, CA, United States
Corley, Neil C., Mountain View, CA, United States
PA Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)
PI US 6074844 20000613
AI US 1997-872979 19970611 (8)
DT Utility
FS Granted
LN.CNT 2637
INCL INCLM: 435/069.100
INCLS: 435/325.000; 435/252.300; 435/320.100; 536/023.500; 536/023.100
NCL NCLM: 435/069.100
NCLS: 435/252.300; 435/320.100; 435/325.000; 536/023.100; 536/023.500
IC [7]
ICM: C12N015-12
ICS: C12N015-63; C12N015-85
EXF 536/23.4; 536/23.5; 536/23.1; 435/69.1; 435/325; 435/252.3; 435/320.1
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 4 OF 11 USPATFULL
AN 1999:96050 USPATFULL
TI Solid active extrusion compound preparations containing low-substituted hydroxypropylcellulose
IN Grabowski, Sven, Ludwigshafen, Germany, Federal Republic of
Breitenbach, Jorg, Mnnheim, Germany, Federal Republic of
Rosenberg, Joerg, Ellerstadt, Germany, Federal Republic of
Sanner, Axel, Frankenthal, Germany, Federal Republic of
PA BASF Aktiengesellschaft, Ludwigshafen, Germany, Federal Republic of (non-U.S. corporation)
PI US 5939099 19990817
WO 9625151 19960822
AI US 1997-875514 19970730 (8)
WO 1996-EP417 19960201
19970730 PCT 371 date
19970730 PCT 102(e) date
PRAI DE 1995-19504832 19950214
DT Utility
FS Granted
LN.CNT 297
INCL INCLM: 424/488.000
INCLS: 514/781.000
NCL NCLM: 424/488.000
NCLS: 514/781.000
IC [6]
ICM: A61K009-10
ICS: A61K047-38
EXF 424/484; 424/488; 424/499; 424/468; 424/457; 264/464; 264/46.1
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 5 OF 11 USPATFULL
AN 1998:115714 USPATFULL

TI Pharmaceutical dipeptide compositions and methods of use thereof: immunodepressants
IN Khavinson, Vladimir Kh., St. Petersburg, Russian Federation
Morozov, Vyacheslav G., St. Petersburg, Russian Federation
PA Cytran, Inc., Kirkland, WA, United States (U.S. corporation)
PI US 5811399 19980922
AI US 4509048 19950526 (8)
RLI Continuation-in-part of Ser. No. 278463, filed on 21 Jul 1994, now abandoned And Ser. No. 337341, filed on 10 Nov 1994, now patented, Pat. No. 5538951 which is a continuation-in-part of Ser. No. 257495, filed on 7 Jun 1994, now abandoned which is a continuation of Ser. No. 783518, filed on 28 Oct 1991, now abandoned which is a continuation-in-part of Ser. No. 678129, filed on 1 Apr 1991, now abandoned which is a continuation-in-part of Ser. No. 415283, filed on 30 Aug 1989, now abandoned
DT Utility
FS Granted
LN.CNT 8863
INCL INCLM: 514/019.000
INCLS: 514/011.000
NCL NCLM: 514/019.000
NCLS: 514/011.000
IC [6]
ICM: A61K038-00
EXF 514/11; 514/19
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 6 OF 11 USPATFULL
AN 1998:154268 USPATFULL
TI Multi-faceted method to repress reproduction of latent viruses in humans
and animals
IN Van Dyke, Knox, Morgantown, WV, United States
PA HIV Diagnostics, Inc., Lexington, KY, United States (U.S. corporation)
PI US 5846961 19981208
AI US 1995-479010 19950607 (8)
RLI Division of Ser. No. US 1994-317730, filed on 4 Oct 1994, now patented, Pat. No. US 5686436 which is a continuation-in-part of Ser. No. US 1993-61573, filed on 13 May 1993, now abandoned
DT Utility
FS Granted
LN.CNT 1213
INCL INCLM: 514/171.000
INCLS: 514/198.000; 514/369.000; 514/374.000; 514/378.000; 514/561.000; 514/563.000
NCL NCLM: 514/171.000
NCLS: 514/198.000; 514/369.000; 514/374.000; 514/378.000; 514/561.000; 514/563.000
IC [6]
ICM: A61K031-56
ICS: A61K031-43; A61K031-425
EXF 314/450; 514/171; 514/198; 514/369; 514/374; 514/375; 514/561; 514/563
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 7 OF 11 USPATFULL
AN 1998:111911 USPATFULL
TI Method for treatment of purulent inflammatory diseases
IN Morozov, Vyacheslav G., St. Petersburg, Russian Federation
Khavinson, Vladimir Kh., St. Petersburg, Russian Federation
PA Cytoven J.V., Kirkland, WA, United States (U.S. corporation)

PI US 5807830 19980915
AI US 1995-452061 19950526 (8)
RLI Continuation-in-part of Ser. No. US 1994-337341, filed on 10 Nov 1994, now patented, Pat. No. US 5538951 And a continuation-in-part of Ser. No. US 1994-278463, filed on 21 Jul 1994, now abandoned which is a continuation-in-part of Ser. No. US 1994-257495, filed on 7 Jun 1994, now abandoned which is a continuation of Ser. No. US 1991-783518, filed on 28 Oct 1991, now abandoned which is a continuation-in-part of Ser. No. US 1991-678129, filed on 1 Apr 1991, now abandoned which is a continuation-in-part of Ser. No. US 1989-415283, filed on 30 Aug 1989, now abandoned
PRAI SU 1987-4352833 19871230
DT Utility
FS Granted
LN.CNT 8879
INCL INCLM: 514/019.000
INCLS: 514/015.000; 514/016.000; 514/017.000; 514/018.000; 424/184.100; 424/185.100; 424/278.100
NCL NCLM: 514/019.000
NCLS: 424/184.100; 424/185.100; 424/278.100; 514/015.000; 514/016.000; 514/017.000; 514/018.000
IC [6]
ICM: A61K038-00
ICS: A61K031-00; A61K045-00
EXF 514/19; 514/18; 514/17; 514/16; 514/15; 514/11; 424/184.1; 424/185.1; 424/278.1
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 8 OF 11 USPATFULL
AN 1998:72601 USPATFULL
TI Pharmaceutical dipeptide compositions and methods of use thereof: systemic toxicity
IN Morozov, Vyacheslav G., St. Petersburg, Russian Federation
Khavinson, Vladimir Kh., St. Petersburg, Russian Federation
PA Cytran, Inc., Kirkland, WA, United States (U.S. corporation)
PI US 5770576 19980623
AI US 1995-452077 19950526 (8)
RLI Continuation of Ser. No. US 1994-337341, filed on 10 Nov 1994, now patented, Pat. No. US 5538951 which is a division of Ser. No. US 1989-415283, filed on 30 Aug 1989 And a continuation-in-part of Ser. No. US 1994-278463, filed on 21 Jul 1994, now abandoned which is a continuation-in-part of Ser. No. US 1994-257495, filed on 7 Jun 1994, now abandoned which is a continuation of Ser. No. US 1991-783518, filed on 28 Oct 1991, now abandoned which is a continuation-in-part of Ser. No. US 1991-678129, filed on 1 Apr 1991, now abandoned which is a continuation-in-part of Ser. No. US 1989-415283, filed on 30 Aug 1989, now abandoned
DT Utility
FS Granted
LN.CNT 8823
INCL INCLM: 514/019.000
INCLS: 514/011.000
NCL NCLM: 514/019.000
NCLS: 514/011.000
IC [6]
ICM: A61K038-00
EXF 514/11; 514/19
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 9 OF 11 USPATFULL
AN 1998:28061 USPATFULL
TI Methods for normalizing numbers of lymphocytes
IN Morozov, Vyacheslav G., St. Petersburg, Russian Federation
Khavinson, Vladimir Kh., St. Petersburg, Russian Federation
PA Cytoven J.V., Kirkland, WA, United States (U.S. corporation)
PI US 5728680 19980317
AI US 1995-452411 19950526 (8)
RLI Continuation-in-part of Ser. No. US 1994-337341, filed on 10 Nov 1994, now patented, Pat. No. US 5538951 And a continuation-in-part of Ser. No.
US 1994-278463, filed on 21 Jul 1994, now abandoned which is a continuation-in-part of Ser. No. US 1994-257495, filed on 7 Jun 1994, now abandoned which is a continuation of Ser. No. US 1991-783518, filed on 28 Oct 1991, now abandoned which is a continuation-in-part of Ser. No. US 1991-678129, filed on 1 Apr 1991, now abandoned which is a continuation-in-part of Ser. No. US 1989-415283, filed on 30 Aug 1989, now abandoned
PRAI SU 1987-4352833 19871230
DT Utility
FS Granted
LN.CNT 8309
INCL INCLM: 514/019.000
INCLS: 514/009.000; 514/011.000
NCL NCLM: 514/019.000
NCLS: 514/009.000; 514/011.000
IC [6]
ICM: A61K038-05
EXF 514/9; 514/11; 514/19
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 10 OF 11 USPATFULL
AN 97:104464 USPATFULL
TI Multi-faceted method to repress reproduction of latent viruses in humans
and animals
IN Van Dyke, Knox, Morgantown, WV, United States
PA HIV Diagnostics, Inc., Lexington, KY, United States (U.S. corporation)
PI US 5686436 19971111
AI US 1994-317730 19941004 (8)
RLI Continuation-in-part of Ser. No. US 1993-61573, filed on 13 May 1993, now abandoned
DT Utility
FS Granted
LN.CNT 1145
INCL INCLM: 514/171.000
INCLS: 514/198.000; 514/369.000; 514/374.000; 514/378.000; 514/561.000; 514/563.000
NCL NCLM: 514/171.000
NCLS: 514/198.000; 514/369.000; 514/374.000; 514/378.000; 514/561.000; 514/563.000
IC [6]
ICM: A61K031-56
ICS: A61K031-43; A61K031-425; A61K031-195
EXF 424/450; 514/171; 514/198; 514/369; 514/374; 514/378; 514/561; 514/563
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 11 OF 11 USPATFULL
AN 97:27180 USPATFULL

```
TI      Compositions containing piperine
IN      Patel, Ramanbhai B., Ahmedabad, India
        Modi, Indravadan A., Ahmedabad, India
PA      Cadila Laboratories Limited, Ahmedabad, India (non-U.S. corporation)
PI      US 5616593              19970401
AI      US 1994-324584          19941018 (8)
PRAI    IN 1993-35693       19931029
DT      Utility
FS      Granted
LN.CNT 636
INCL    INCLM: 514/321.000
        INCLS: 514/328.000
NCL     NCLM:  514/321.000
        NCLS:  514/328.000
IC      [6]
        ICM: A01N043-40
EXF     514/321; 514/328
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


=> d k11 2 kwic
'K11' IS NOT A VALID FORMAT FOR FILE 'USPATFULL'

The following are valid formats:

The default display format is STD.

ABS -------- AB
ALL -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PTERM, DCD,
             RLI, PRAI, DT, FS, REP, REN, EXNAM, LREP, CLMN, ECL,
             DRWN, AB, GOVI, PARN, SUMM, DRWD, DETD, CLM, INCL,
             INCLM, INCLS, NCL, NCLM, NCLS, IC, ICM, ICS, EXF,
             ARTU
ALLG ------- ALL plus PAGE.DRAW
BIB -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PTERM, DCD, RLI,
             PRAI, DT, FS, EXNAM, LREP, CLMN, ECL, DRWN, LN.CNT
CAS -------- OS, CC, SX, ST, IT
CBIB ------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PRAI, DT, FS
DALL ------- ALL, delimited for post-processing
FPALL ------ PI, TI, IN, INA, PA, PAA, PAT, PETRM, DCD, AI,
             RLI, PRAI, IC, ICM, ICS, INCL, INCLM, INCLS, NCL, NCLM,
             NCLS, EXF, REP, REN,ARTU, EXNAM, LREP, CLMN, DRWN, AB,
             PARN, SUMM, DRWD, DETD, CLM
FPBIB ------ PI, TI, IN, INA, PA, PAA, PAT, PTERM, DCD, AI,
             RLI, PRAI, REP, REN, EXNAM, LREP, CLM, CLMN, DRWN
FHITSTR ---- HIT RN, its text modification, its CA index name, and
             its structure diagram
FPG -------- FP plus PAGE.DRAW
GI --------- PN and page image numbers
HIT -------- All fields containing hit terms
HITRN ------ HIT RN and its text modification
HITSTR ----- HIT RN, its text modification, its CA index name, and
             its structure diagram
IABS ------- ABS, indented with text labels
IALL ------- ALL, indented with text labels
IALLG ------ IALL plus PAGE.DRAW
IND -------- INCL, INCLM, INCLS, NCL, NCLM, NCLS, IC, ICM, ICS,
             EXF, ARTU, OS, CC, SX, ST, IT
ISTD ------- STD, indented with text labels
KWIC ------- All hit terms plus 20 words on either side
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MAX -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, PTERM, DCD, RLI, PRAI, DT, FS, REP, REN, EXNAM, LREP, CLMN, ECL, DRWN, AB, GOVI, PARN, SUMM, DRWD, DETD, CLM, INCL, INCLM, INCLS, NCL, NCLM, NCLS, IC, ICM, ICS, EXF, ARTU OS, CC, SX, ST, IT

SBIB ------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, RLI, PRAI, DT, FS, LN.CNT

SCAN ------- AN, TI, NCL, NCLM, NCLS, IC, ICM, ICS (random display without answer number. SCAN must be entered on the same line as DISPLAY, e.g., D SCAN)

STD -------- AN, TI, IN, INA, PA, PAA, PAT, PI, AI, RLI, PRAI, DT, FS, LN.CNT, INCL, INCLM, INCLS, NCL, NCLM, NCLS, IC, ICM, ICS, EXF (STD is the default)

TRIAL ------ AN, TI, INCL, INCLM, INCLS, NCL, NCLM, NCLS, IC, ICM, ICS

The DISPLAY BROWSE command allows the user to move forward and backward within a document, and search for a particular character string within a document display. To do this, enter one of the following at the colon prompt (:).

F ---------- move forward to the next field or paragraph
Fn ---------- move forward n fields or paragraphs
B ---------- move backward to the next field or paragraph
Bn ---------- move backward n fields or paragraphs
SEA term ---- search for the next instance of term
SEA- term --- search backwards for the last instance of term

BIBG ------- BIB plus PAGE.DRAW

FP --------- PI, TI, IN, INA, PA, PAA, PAT, PTERM, DCD, AI, RLI, PRAI, IC, ICM, ICS, INCL, INCLM, INCLS, NCL, NCLM, NCLS, EXF, REP, REN, ARTU, EXNAM, LREP, CLMN, DRWN, AB

IBIB ------- BIB, indented with text labels
IBIBG ------ IBIB plus PAGE.DRAW
IMAX ------- MAX, indented with text labels
OCC -------- List of display fields containing hit terms and number of occurrences in each field

The order of the fields for F and B is the same as the order in the ALL format. If term is not specified when using the SEA option, the term entered in the previous search request is used. Note that SEA makes no distinction between upper and lower case letters.

ENTER DISPLAY FORMAT (STD):kwic

L11 ANSWER 2 OF 11 USPATFULL

SUMM U.S. Pat. No. 5,607,693 issued Mar. 4, 1997 to Bonte et al. discloses a cosmetic or **pharmaceutical composition** which comprises oxyacanthine, one of its derivatives, one of their cosmetically or pharmaceutically acceptable acid addition salts or an extract. . .

SUMM . . . metal, alkaline earth metal and/or ammonium salts of thiocyanic acid in combination with B) at lease one component selected from **estrogens**, sulfur, sulfide ions, vasodilators, skin-active vitamins, inorganic selenium compounds, amino acids, protein hydrolyzates and carboxylic acids physiologically occurring in the. . .

DETD . . . include one or more of kelp, alfalfa, Vitamins A and E, iron, ginseng, and acidophilus apple pectin, silica, or a **multivitamin**

as currently available, in **tablet** or other forms, in the market.

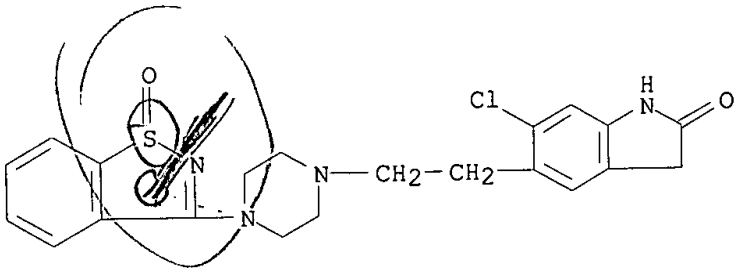
DETD . . . example, the booster includes about 1 teaspoon apple cider vinegar, 1 oz water and 1 oz honey taken with a **multivitamin** and 8000 I.U. Vitamin A and 1000 I.U. Vitamin E as available from Spring Valley, taken once daily. In addition,. . .

DETD . . . the present invention. Hair still growing with lots of new breakout all over heard. Begin using Silicea 6.times. with 4 **tablets** daily dissolved in spring water. Temple area of scalp beginning to grow out nicely.

CLM What is claimed is:

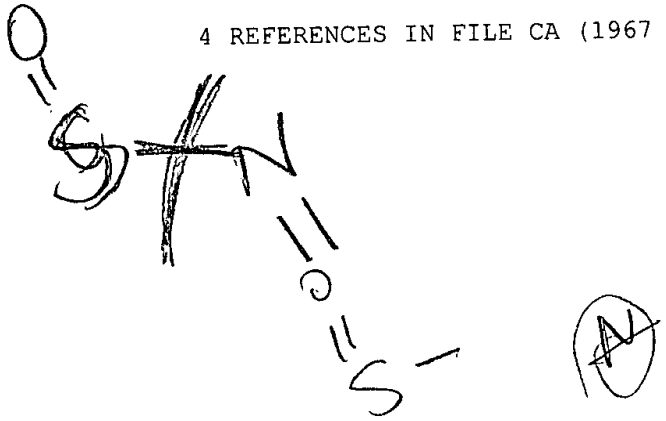
. . . claim 8 further comprising the step of (d) administering orally a booster selected from the group consisting of vinegar, honey, **multivitamin tablet**, Vitamin A, Vitamin E, Alfafa, Acidophillus Rexal, Kelp, silca, ginseng, and a combination thereof.

L8 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 188797-80-0 REGISTRY
CN 2H-Indol-2-one,
6-chloro-1,3-dihydro-5-[2-[4-(1-oxido-1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Ziprasidone sulfoxide**
FS 3D CONCORD
MF C21 H21 Cl N4 O2 S
SR CA
LC STN Files: CA, CAPLUS, TOXLIT



2. Sulfone
188797-77-5

4 REFERENCES IN FILE CA (1967 TO DATE)



L1 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2001 ACS
AN 2000:263306 CAPLUS
DN 133:68333
TI Identification of the major human liver cytochrome P450 isoform(s) responsible for the formation of the primary metabolites of ziprasidone and prediction of possible drug interactions
AU Prakash, C.; Kamel, A.; Cui, D.; Whalen, R. D.; Miceli, J. J.; Tweedie, D.
CS Department of Drug Metabolism, Pfizer Central Research, Groton, CT, 06340, USA
SO Br. J. Clin. Pharmacol. (2000), 49(Suppl. 1), 35S-42S
CODEN: BCPHBM; ISSN: 0306-5251
PB Blackwell Science Ltd.
DT Journal
LA English
RE.CNT 30
RE
(4) Howard, H; J Labelled Compd Radiopharm 1994, V34, P117 CAPLUS
(7) Kronbach, T; Meth Enzymol 1991, V206, P509 CAPLUS
(8) Meier, U; Anal Biochem 1985, V151, P286 CAPLUS
(10) Nelson, D; DNA Cell Biol 1993, V12, P1 CAPLUS
(11) Newton, D; Drug Metab Dispos 1995, V23, P154 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d 2 kwic

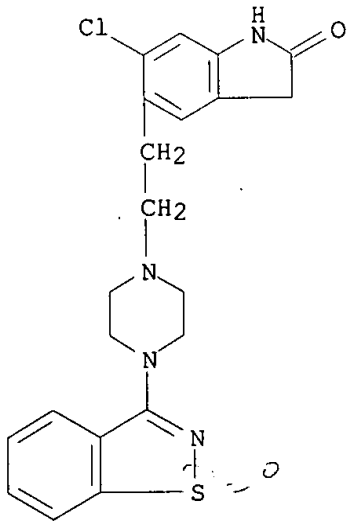
L1 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2001 ACS
AB . . . detd. using human liver microsomes from three subjects. Mean Ki values were calcd. Results Three CYP-mediated metabolites - ziprasidone sulfoxide, **ziprasidone sulfone** and oxindole acetic acid-were identified. The apparent Km and Vmax values for the formation of the major metabolite, ziprasidone sulfoxide. . .

=> d 2 ab

L1 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2001 ACS
AB The aim of this study was to identify the cytochrome P 450 (CYP) isoform(s) responsible for the formation of the primary metabolite of ziprasidone (ziprasidone sulfoxide), to det. the kinetics of its formation and to predict possible drug interactions by investigating CYP isoform inhibition in an in vitro study. Methods In vitro metab. of [14C]-ziprasidone was studied using human liver microsomes. The metabolites were identified using mass spectrometry. The kinetics of metabolite formation were detd. using [14C]-ziprasidone (10-200 .mu.M) over 5 min, and Km and Vmax were estd. from Lineweaver-Burk plots. IC50 values for the inhibition of specific probe substrates for CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, by ziprasidone, risperidone and 9-hydroxyrisperidone were also detd. using human liver microsomes from three subjects. Mean Ki values were calcd. Results Three CYP-mediated metabolites - ziprasidone sulfoxide, **ziprasidone sulfone** and oxindole acetic acid-were identified. The apparent Km and Vmax values for the formation of the major metabolite, ziprasidone sulfoxide (measured

as the sum of sulfoxide and sulfone) were 235 .mu.M and 1.14 nmol mg-1 protein min-1, resp. Isoform-selective inhibitors and recombinant enzymes indicated that CYP3A4 is responsible for the formation of ziprasidone metabolites. Ziprasidone was not a substrate for the other isoforms studied. Similar in vitro inhibition of CYP2D6 (Ki 6.9-16 .mu.M) and CYP3A4 (Ki 64-80 .mu.M) was obtained with ziprasidone, risperidone and 9-hydroxyrisperidone. The in vivo free drug concns. assocd. with clin. EDs of ziprasidone are at least 1500-fold lower than the mean Ki for either CYP2D6 inhibition or CYP3A4 inhibition. Conclusions Ziprasidone is predominantly metabolized by CYP3A4 in human liver microsomes and is not expected to mediate drug interactions with coadministered CYP substrates, at clin. EDs.

L11 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 146939-27-7 REGISTRY
CN 2H-Indol-2-one, 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 5-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one
CN 5-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-2-indolinone
CN CP 88059
CN **Ziprasidone**
FS 3D CONCORD
MF C21 H21 Cl N4 O S
CI COM
SR World Health Organization
LC STN Files: ADISINSIGHT, ANABSTR, BIOBUSINESS, BIOSIS, CA, CAPLUS, CASREACT, CBNB, CIN, DRUGNL, DRUGPAT, DRUGUPDATES, IPA, MEDLINE, MRCK*, PHAR, PROMT, SYNTHLINE, TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO



99 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
99 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L5 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2002 ACS
AB A review with 24 refs. Ziprasidone is a novel antipsychotic drug. It has high affinity for serotonin 5-**HT2** and **dopamine** D2 receptors in vitro, with an 11-fold higher affinity for 5-**HT2** than for D2 receptors, suggestive of a low potential for inducing motor disturbance [including extrapyramidal symptoms (EPS)]. The effects of ziprasidone in receptor binding studies reflected its in vitro pharmacol., with more potent effects against 5-**HT2** receptor-than against D2 receptor-mediated behavior. Because ziprasidone inhibits serotonin (5-hydroxytryptamine; 5-HT) and noradrenaline (norepinephrine) reuptake, it may have anxiolytic and antidepressant effects. Data from phase II and III clin. trials have shown ziprasidone to be effective in reducing the pos. and neg. symptoms of, and depression assocd. with, schizophrenia, and in reducing anxiety in patients about to undergo dental surgery. Ziprasidone was generally well tolerated in phase II and III clin. trials, with somnolence and nausea being the most frequently reported adverse events in placebo-controlled studies. Motor disturbances, including EPS, were infrequently obsd.
AN 1997:593623 CAPLUS
DN 127:242699
TI Ziprasidone
AU Davis, Rick; Markham, Anthony
CS Adis International Limited, Auckland, N. Z.
SO CNS Drugs (1997), 8(2), 153-159
CODEN: CNDREF; ISSN: 1172-7047
PB Adis
DT Journal; General Review
LA English
AB A review with 24 refs. Ziprasidone is a novel antipsychotic drug. It has high affinity for serotonin 5-**HT2** and **dopamine** D2 receptors in vitro, with an 11-fold higher affinity for 5-**HT2** than for D2 receptors, suggestive of a low potential for inducing motor disturbance [including extrapyramidal symptoms (EPS)]. The effects of ziprasidone in receptor binding studies reflected its in vitro pharmacol., with more potent effects against 5-**HT2** receptor-than against D2 receptor-mediated behavior. Because ziprasidone inhibits serotonin (5-hydroxytryptamine; 5-HT) and noradrenaline (norepinephrine) reuptake, it may have anxiolytic and antidepressant effects. Data from phase II and III clin. trials have shown ziprasidone to be effective in reducing the pos. and neg. symptoms of, and depression assocd. with, schizophrenia, and in reducing anxiety in patients about to undergo dental surgery. Ziprasidone was generally well tolerated in phase II and III clin. trials, with somnolence and nausea being the most frequently reported adverse events in placebo-controlled studies. Motor disturbances, including EPS, were infrequently obsd.
IT **146939-27-7**, Ziprasidone
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ziprasidone for psychotic disorders)

```
       ICS: A61K031-495
EXF    544/360; 514/255
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


=> s l2 and neuroleptic disorder
          1925 NEUROLEPTIC
          1072 NEUROLEPTICS
          2420 NEUROLEPTIC
                 (NEUROLEPTIC OR NEUROLEPTICS)
         25176 DISORDER
         44314 DISORDERS
         54576 DISORDER
                 (DISORDER OR DISORDERS)
            53 NEUROLEPTIC DISORDER
                 (NEUROLEPTIC(W)DISORDER)
L5           0 L2 AND NEUROLEPTIC DISORDER

=> s l2 and neuroleptic
          1925 NEUROLEPTIC
          1072 NEUROLEPTICS
          2420 NEUROLEPTIC
                 (NEUROLEPTIC OR NEUROLEPTICS)
L6          16 L2 AND NEUROLEPTIC

=> s l6 and py<1999
       2431197 PY<1999
L7           7 L6 AND PY<1999

=> d l7 1-7

L7   ANSWER 1 OF 7  USPATFULL
AN     2001:71539  USPATFULL
TI     Inclusion complexes of aryl-heterocyclic salts
IN     Kim, Yesook, Branford, CT, United States
       Johnson, Kevin C., Niantic, CT, United States
       Shanker, Ravi M., Groton, CT, United States
PA     Pfizer Inc., New York, NY, United States (U.S. corporation)
PI     US 6232304          B1   20010515
       WO 9741896          19971113                                    <--
AI     US 1998-147239           19981105 (9)
       WO 1997-IB321            19970401
                                19981105  PCT 371 date
                                19981105  PCT 102(e) date
PRAI   US 1996-19204P      19960507 (60)
DT     Utility
FS     Granted
LN.CNT 719
INCL   INCLM: 514/058.000
       INCLS: 544/368.000; 536/103.000
NCL    NCLM:  514/058.000
       NCLS:  536/103.000; 544/368.000
IC     [7]
       ICM: A61K047-48
EXF    536/103; 514/58; 544/368
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7   ANSWER 2 OF 7  USPATFULL
AN     1998:98932  USPATFULL
TI     DHA-pharmaceutical agent conjugates of taxanes
```

IN Shashoua, Victor E., Brookline, MA, United States
Swindell, Charles S., Merion, PA, United States
Webb, Nigel L., Bryn Mawr, PA, United States
Bradley, Matthews O., Laytonsville, MD, United States
PA Neuromedica, Inc., Conshohocken, PA, United States (U.S. corporation) <--
PI US 5795909 19980818
AI US 1996-651312 19960522 (8)
DT Utility
FS Granted
LN.CNT 2451
INCL INCLM: 514/449.000
INCLS: 514/549.000
NCL NCLM: 514/449.000
NCLS: 514/549.000
IC [6]
ICM: A61K031-335
ICS: A61K031-22
EXF 514/449; 514/549
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 3 OF 7 USPATFULL
AN 94:71127 USPATFULL
TI Process for preparing aryl piperazinyl-heterocyclic compounds with a piperazine salt
IN Busch, Frank R., Gales Ferry, CT, United States
Bowles, Paul, Groton, CT, United States
John, Douglas, New London, CT, United States
Allen, Meldrum, Uncasville, CT, United States
DiRoma, Sabeto A., Glastonbury, CT, United States
Godek, Dennis M., Glastonbury, CT, United States
PA Pfizer Inc., New York, NY, United States (U.S. corporation)
PI US 5338846 19940816 <--
AI US 1993-49905 19930420 (8)
RLI Continuation-in-part of Ser. No. US 1992-936179, filed on 26 Aug 1992, now patented, Pat. No. US 5206366 And Ser. No. US 1992-939204, filed on 1 Sep 1992
DT Utility
FS Granted
LN.CNT 371
INCL INCLM: 544/368.000
NCL NCLM: 544/368.000
IC [5]
ICM: C07D417-06
ICS: C07D413-06
EXF 544/368
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 4 OF 7 USPATFULL
AN 94:42452 USPATFULL
TI Monohydrate of 5-(2-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-ethyl)-6-chloro-1,3-dihydro-2H-indol-2-one-hydrochloride
IN Allen, Douglas J. M., New London, CT, United States
Busch, Frank R., Gales Ferry, CT, United States
DiRoma, Sabeto A., Uncasville, CT, United States
Godek, Dennis M., Glastonbury, CT, United States
PA Pfizer Inc., New York, NY, United States (U.S. corporation)
PI US 5312925 19940517 <--
AI US 1992-939204 19920901 (7)
DT Utility

FS Granted
LN.CNT 193
INCL INCLM: 544/368.000
NCL NCLM: 544/368.000
IC [5]
ICM: C07D417-14
EXF 544/368; 514/254
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 5 OF 7 USPATFULL
AN 93:33619 USPATFULL
TI Process for preparing aryl piperazinyl-heterocyclic compounds
IN Bowles, Paul, Groton, CT, United States
PA Pfizer Inc., New York, NY, United States (U.S. corporation)
PI US 5206366 19930427 <--
AI US 1992-936179 19920826 (7)
DT Utility
FS Granted
LN.CNT 274
INCL INCLM: 544/368.000
INCLS: 544/230.000; 544/284.000; 544/363.000; 544/366.000; 544/373.000; 544/376.000
NCL NCLM: 544/368.000
NCLS: 544/230.000; 544/284.000; 544/363.000; 544/366.000; 544/373.000; 544/376.000
IC [5]
ICM: C07D417-06
ICS: C07D413-06
EXF 544/230; 544/284; 544/363; 544/368; 544/366; 544/373; 544/376
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 6 OF 7 USPATFULL
AN 89:95740 USPATFULL
TI Piperazinyl-heterocyclic compounds
IN Lowe, III, John A., Stonington, CT, United States
Nagel, Arthur A., Gales Ferry, CT, United States
PA Pfizer Inc., New York, NY, United States (U.S. corporation)
PI US 4883795 19891128 <--
AI US 1989-300995 19890123 (7)
RLI Division of Ser. No. US 1988-146886, filed on 22 Jan 1988, now patented,
Pat. No. US 4831031
DT Utility
FS Granted
LN.CNT 773
INCL INCLM: 514/253.000
INCLS: 514/254.000; 544/230.000; 544/237.000; 544/284.000; 544/362.000; 544/363.000; 544/366.000; 544/368.000; 544/373.000; 544/392.000
NCL NCLM: 514/252.170
NCLS: 514/252.150; 514/253.050; 514/253.060; 514/254.020; 514/254.040; 514/254.060; 544/230.000; 544/237.000; 544/284.000; 544/362.000; 544/363.000; 544/366.000; 544/368.000; 544/373.000; 544/392.000
IC [4]
ICM: A61K031-495
ICS: C07D263-58; C07D235-26; C07D413-12
EXF 544/362; 544/363; 544/366; 544/368; 544/373; 544/230; 544/284; 544/237; 544/392; 514/253; 514/254
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 7 OF 7 USPATFULL

AN 89:38970 USPATFULL
TI Aryl piperazinyl-(C.sub.2 or C.sub.4) alkylene heterocyclic compounds having **neuroleptic** activity
IN Lowe, III, John A., Stonington, CT, United States
Nagel, Arthur A., Gales Ferry, CT, United States
PA Pfizer Inc., New York, NY, United States (U.S. corporation)
PI US 4831031 19890516 <--
AI US 1988-146886 19880122 (7)
DT Utility
FS Granted
LN.CNT 772
INCL INCLM: 514/254.000
INCLS: 514/253.000; 544/230.000; 544/237.000; 544/284.000; 544/359.000; 544/363.000; 544/366.000; 544/367.000; 544/368.000; 544/372.000; 544/373.000
NCL NCLM: 514/254.020
NCLS: 514/252.170; 514/253.050; 514/253.060; 514/254.040; 514/254.090; 544/230.000; 544/237.000; 544/284.000; 544/359.000; 544/363.000; 544/366.000; 544/367.000; 544/368.000; 544/372.000; 544/373.000
IC [4]
ICM: A61K031-495
ICS: C07D417-14
EXF 544/368; 544/359; 544/363; 544/366; 544/367; 544/372; 544/373; 544/237; 544/284; 544/230; 544/368; 514/254; 514/253; 514/254
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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L4   ANSWER 1 OF 2  USPATFULL
AN     2001:86466  USPATFULL
TI     Mesylate dihydrate salts of 5-(2-(4-(1,2-benzisothiazol-3-yl)-1-
       piperazinyl)-ethyl)-6-chloro-1,3-dihydro-2(1H)-indol-2-one
       (=ziprasidone), its preparation and its use as dopamine D2 antagonist
IN     Busch, Frank R., Gales Ferry, CT, United States
       Rose, Carol A., Ledyard, CT, United States
       Shine, Russell J., Waterford, CT, United States
PA     Pfizer Inc, New York, NY, United States (U.S. corporation)
PI     US 6245765          B1   20010612
       WO 9742191          19971113                                    <--
AI     US 1999-180455           19990830 (9)
       WO 1997-IB393            19970410
                                19990830  PCT 371 date
                                19990830  PCT 102(e) date
PRAI   US 1996-16757P      19960507 (60)
DT     Utility
FS     GRANTED
LN.CNT 455
INCL   INCLM: 514/252.130
       INCLS: 514/254.040; 514/254.090; 544/368.000; 544/376.000; 544/358.000;
              548/469.000; 548/503.000; 548/212.000; 548/214.000
NCL    NCLM:  514/252.130
       NCLS:  514/254.040; 514/254.090; 544/358.000; 544/368.000; 544/376.000;
              548/212.000; 548/214.000; 548/469.000; 548/503.000
IC     [7]
       ICM: A61K031-495
       ICS: A61K031-50; C07D209-04; C07D275-04; C07D417-00
EXF    544/376; 544/358; 544/368; 514/254.04; 514/254.09; 514/252.13; 548/469;
       548/503; 548/212; 548/214
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


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L4   ANSWER 2 OF 2  USPATFULL
AN     2000:113945  USPATFULL
TI     Mesylate trihydrate salt of 5-(2-(4-(1,2-benzisothiazol-3-yl)-1-
       piperazinyl)ethyl)-6-chloro-1,3-dihy dro-2(1H)-indol-2-one
       (=ziprasidone), its preparation and its use as dopamine D2 antagonist
IN     Busch, Frank R., Gales Ferry, CT, United States
       Rose, Carol A., Ledyard, CT, United States
PA     Pfizer Inc, New York, NY, United States (U.S. corporation)
PI     US 6110918               20000829
       WO 9742190          19971113                                    <--
AI     US 1999-180456           19990302 (9)
       WO 1997-IB306            19970326
                                19990302  PCT 371 date
                                19990302  PCT 102(e) date
PRAI   US 1996-16537P      19960507 (60)
DT     Utility
FS     Granted
LN.CNT 387
INCL   INCLM: 514/255.000
       INCLS: 544/360.000
NCL    NCLM:  514/254.040
       NCLS:  544/360.000
IC     [7]
       ICM: A01N043-60
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